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(54) Title: SUBSTITUTED POLYAMINE COMPOUNDS

(57) Abstract: The invention provides a compound represented by the general forumla (I), wherein $R^1$, $R^2$, $R^3$, $R^6$, $R^7$, p, A, B and D are as defined in the description. The compounds are useful as AMPA antagonists.

**Substituted Polyamine Compounds**

The present invention provides substituted polyamines, which are potent AMPA antagonists. The compounds are potentially useful in the treatment of a number of diseases responsive to the AMPA receptor.

**Background of the Invention.**

Glutamic acid, or glutamate, is the major excitatory amino acid neurotransmitter in the mammalian central nervous system (CNS) and acts through two classes of receptors, the ionotropic and metabotropic receptors. The ionotropic glutamate receptors (iGluRs) are divided into three subtypes based on the affinities of agonists for these receptors, namely *N*-methyl-D-aspartate (NMDA), (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) and kainic acid (or kainate) receptors. The iGluRs are particularly interesting as there is strong evidence that glutamate-induced excessive $Ca^{2+}$ entry under pathophysiological conditions leads to a wide range of neurological insults including ischemia, trauma, hypoglycaemia and epileptic seizures, and iGluRs might also be involved in chronic neurodegenerative disorders such as Alzheimer's disease, Huntington's chorea, AIDS encephalopathy and amyotrophic lateral sclerosis (Ozawa et al. *Prog. Neurobiol.* **1998**, *54*, 581-618; Dingledine et al. *Pharmacol. Rev.* **1999**, *51*, 7-62; Danysz and Parsons *Pharmacol. Rev.* **1998**, *50*, 597-664; Bleakman and Lodge *Neuropharmacol.* **1998**, *37*, 1187-1204; Parsons et al. *Drugs News & Perspectives* **1998**, *11*, 523-569; Pellegrini-Giampetro et al. *TINS* **1997**, *20*, 464-470). Other diseases responsive to the AMPA receptor are described in Lees et al. *Drugs* **2000**, *59(1)*, 33-78;

AMPA receptors are distributed ubiquitously throughout the CNS and mediate fast excitatory neurotransmission. Although most native AMPA receptors exhibit low $Ca^{2+}$ permeability, AMPA receptors with high $Ca^{2+}$ permeability have been reported in a variety of cells in the CNS, a property that is inversely correlated with the relative abundance of the GluR2 subunit. There is increasing evidence that $Ca^{2+}$-permeable AMPA receptors play a part in the pathogenesis of neurological disorders (Pellegrini-Giampetro et al. *TINS* **1997**, *20*, 464-470; Weiss and Sensi, *TINS* **2000**, 23, 365-371; Gill and Lodge in *Int. Rev. Neurobiol.*, Green and

Cross, Eds., Academic Press (San Diego) **1997**, *40*, 197-232). The use of a neuroprotective agent, such as an AMPA receptor antagonist, is believed to be useful in treating disorders and/or reducing the amount of neurological damage associated with these disorders.

Philanthotoxin-433 (PhTX-433) is a polyamine toxin composed of thermospermine, tyrosine and butyric acid. This toxin, which was isolated from the venom of the Egyptian solitary digger wasp, *Philanthus triangulum*, (Eldefrawi et al. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4910-4913), and its synthetic analogue, PhTX-343, non-competitively antagonise a wide range of ionotropic receptors that gate cation-selective ion channels, such as muscle and neuronal nicotinic acetylcholine receptors (nAChRs) (Piek and Hue *Comp. Biochem. Physiol.* **1989**, *93C*, 403-306; Anis et al. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 764-773; Benson et al. *Comp. Biochem. Physiol.* **1993**, *105C*, 303-310; Nakanishi et al. *Bioorg. Med. Chem.* **1997**, *5*, 1969-1988) and ionotropic glutamate receptors (Eldefrawi et al. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4910-4913; Anis et al. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 764-773; Bruce et al. *Toxicon* **1990**, *28*, 1333-1346; Jones et al. *Br. J. Pharmacol.* **1990**, *101*, 968-970; Karst et al. *Comp. Biochem. Physiol.* **1991**, *98C*, 471-477; Karst and Piek *Comp. Biochem. Physiol.* **1991**, *98C*, 479-489; Brackley et al. *J. Pharmacol. Exp. Ther.* **1993**, *266*, 1573-1580; Washburn and Dingledine *J. Pharmacol. Exp. Ther.* **1996**, *278*, 669-678; Huang et al. *Tetrahedron* **1997**, *53*, 12391-12404; Bähring et al. *J. Physiol.* **1997**, *502*, 575-589; Bähring and Mayer *J. Physiol.* **1998**, *509*, 635-650).

Structural analogues of the natural product PhTX-433, most of which contain the (symmetrical) spermine moiety as in PhTX-343, have been synthesised and were used to explore structure-activity relationships (Piek and Hue *Comp. Biochem. Physiol.* **1989**, *93C*, 403-306; Anis et al. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 764-773; Benson et al. *Comp. Biochem. Physiol.* **1993**, *105C*, 303-310; Nakanishi et al. *Bioorg. Med. Chem.* **1997**, *5*, 1969-1988; Bruce et al. *Toxicon* **1990**, *28*, 1333-1346; Huang et al. *Tetrahedron* **1997**, *53*, 12391-12404; Goodnow Jr. R et al. *Tetrahedron* **1990**, *46*, 3267-3286; Goodnow Jr. et al. *J. Med. Chem.* **1991**, *34*, 2389-2394; Choi et al. *Tetrahedron* **1992**, *23*, 4793-4822; Kalivretenos and Nakanishi *J. Org. Chem.* **1993**, *58*, 6596-6608; Choi et al. *Tetrahedron* **1993**, *49*, 5777-5790; Huang et al. *Heterocycles* **1996**, *42*, 723-736). The results of these investigations emphasize

the importance of the hydrophobic character of the tyrosine-butyryl moiety for the activity at nAChR and iGluRs sensitive to quisqualate (quisR).

Other philanthotoxin derivatives have previously been reported and some references are given above. Further, WO 89/07098 describes philanthotoxin analogues which are derivatives of the amino acid tyrosine; WO 9622962 describes other philanthotoxin analogues. None of these compounds are described as potent AMPA antagonists.

Recent studies with PhTX-343-analogues at cloned kainate (Bowie and Mayer *J. Neurosci.* **1998**, *18*, 8175-8185; Bähring et al. *J. Physiol. (Lond.)* **1997**, *502*, 575-589; Bähring and Mayer *J. Physiol. (Lond.)* **1998**, *509*, 635-650) and AMPA (Brackley et al. *J. Pharmacol. Exp. Ther.* **1993**, *266*, 1573-1580; Washburn and Dingledine *J. Pharmacol. Exp. Ther.* **1996**, *278*, 669-678) receptors showed a weak inhibition of $Ca^{2+}$-permeable kainate and AMPA receptors.

Certain philanthotoxin analogues have been prepared, which exhibit enhanced antagonist activity at mammalian muscle-type nAChR, while being inactive on several types of iGluR (Strømgaard et al. *J. Med. Chem.* **1999**, *42*, 5224-5234; Strømgaard et al. *Chirality* **2000**, *12*, 93-102).

Recent studies have shown that the antagonist effects of the substituted polyamine derivatives of the invention increase with increasing application periods and thus increasing concentrations of the iGluR agonist kainate. This observation strongly suggests that agonist induced opening of the iGluR-associated ion channel, which results in flux of $Ca^{2+}$ into the neurones, allows these philanthotoxin analogues to penetrate into the channel with subsequent block of the channel. This use-dependent effect mediated by the agonist kainate indicates that the AMPA receptors are involved in this phenomenon.

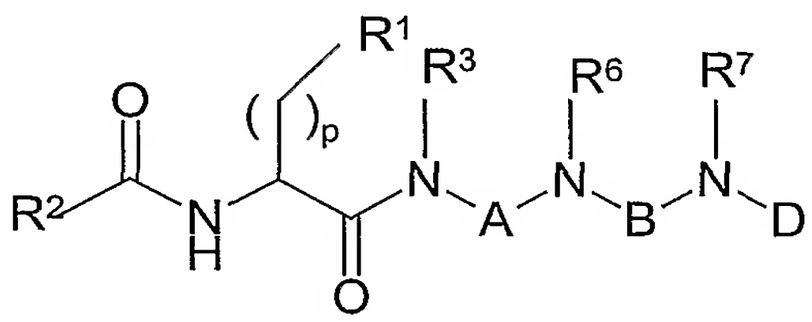
Kainate does activate AMPA as well as kainate receptors, but the effects of kainate at the latter type of receptors desensitise extremely rapidly and this is normally difficult to detect. Kainate activates AMPA receptors in a nondesensitising manner, producing long-lasting activation of this receptor and, thus, a persisting opening of the AMPA receptor associated cation channel. This nondesensitising effect of kainate was observed and used in the present

experiments to demonstrate use-dependent antagonist effects of philanthotoxin analogues. These results clearly indicate that AMPA receptors are the targets of the philanthotoxin antagonists described.

Since excessive release of endogenous glutamate is considered to be a key phenomenon in certain CNS disorders, it is important to develop antagonists for iGluRs, which show particular activity in regions of the brain with elevated levels of glutamate. The present invention provides potent and selective AMPA antagonistic substituted polyamine derivatives. Selective AMPA antagonists will provide more efficient treatment of conditions arising from excessive stimulation of the AMPA receptor. Furthermore, as mentioned previously, pharmacological results indicate that some of the compounds of the present invention, in addition, are use-dependent AMPA antagonists.

**Summary of the Invention**

The present invention provides substituted polyamine derivatives of the general formula I



**I**

wherein

$R^1$ represents a partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms, an aryl or a heteroaryl, all of which may be substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkylthio, $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl, aryl, heteroaryl, wherein aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$ hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; $NR^8R^9$ wherein $R^8$ and $R^9$ independently represent hydrogen, $C_{1-6}$-alkyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, or $R^8$ and $R^9$

together form a ring which may optionally contain further nitrogen, oxygen or sulfur atoms and which may be partly saturated;

p is 0, 1, 2 , 3 or 4;

$R^2$ represents hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$-alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

$R^3$, $R^6$ and $R^7$ independently represent hydrogen or $C_{1-6}$-alkyl;

**A** and **B** independently represent $-(CH_2)_nX(CH_2)_m-$, wherein X represents $-CR^4R^5$, O, or S, wherein $R^4$ and $R^5$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; n is 0-12 and m is 0-12 with the proviso that $1 \leq n+m \leq 12$ and when X represent O or S then $n \geq 2$ and $m \geq 2$;

**D** represents hydrogen, $C_{1-6}$-alkyl or $-(CH_2)_oY(CH_2)_qNR^{10}R^{11}$, wherein Y represents $-CR^{12}R^{13}$, O or S, wherein $R^{12}$ and $R^{13}$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, or $C_{1-6}$-alkoxy; o is 1-12 and q is 1-12 with the proviso that $1 \leq o+q \leq 12$, and when Y represents O or S then $o \geq 2$ and $q \geq 2$; $R^{10}$ and $R^{11}$ independently represent hydrogen or $C_{1-6}$-alkyl;

or a pharmaceutically acceptable addition salt thereof;

The compounds are useful as potent and selective AMPA antagonists.

The invention also provides a pharmaceutical composition comprising at least one compound of Formula I as defined above or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

The invention also provides the use of compounds as above for the manufacture of medicaments for treatment of diseases responsive to antagonists of the AMPA receptor.

The invention provides a method for treatment of diseases responsive to antagonists of the AMPA receptor.

**Detailed Description of the Invention**

Preferred embodiments of the invention are the compounds of formula I, according to the above wherein $R^1$ represents a partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms, an aryl or a heteroaryl, all of which may be substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkylthio, $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl, aryl, heteroaryl, wherein aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; $NR^8R^9$, wherein $R^8$ and $R^9$ independently represent hydrogen, $C_{1-6}$-alkyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, or $R^8$ and $R^9$ together form a ring which may optionally contain further nitrogen, oxygen or sulfur atoms and which may by partly saturated;

p is 0, 1, 2 , 3 or 4; $R^2$ represents $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$-alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

$R^3$, $R^6$ and $R^7$ independently represent hydrogen or $C_{1-6}$-alkyl.

**A** and **B** independently represent $-(CH_2)_nX(CH_2)_m-$, wherein X represents $-CR^4R^5$, O or S, wherein $R^4$ and $R^5$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; n is 0-12 and m is 0-12 with the proviso that $1 \leq n+m \leq 12$ and when X represents O or S then $n \geq 2$ and $m \geq 2$;

**D** represents hydrogen, $C_{1-6}$-alkyl or $-(CH_2)_oY(CH_2)_qNR^{10}R^{11}$, wherein Y represents $-CR^{12}R^{13}$, O or S, wherein $R^{12}$ and $R^{13}$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; o is 1-12 and q is 1-12 with the proviso that $1 \leq o+q \leq 12$, and when Y represents O or S then $o \geq 2$ and $q \geq 2$; $R^{10}$ and $R^{11}$ independently represent hydrogen or $C_{1-6}$-alkyl; with the proviso that when $R^2$ is a 2-

phenylethylene, benzyl, cyclohexyl or phenyl and p is 1, and D is $-(CH_2)_oY(CH_2)_qNR^{10}R^{11}$, wherein Y is $-CR^{12}R^{13}$ and $R^{10}$, $R^{11}$, $R^{12}$ and $R^{13}$ are all hydrogen, then $R^1$ is not phenyl substituted with OH in the 4-position;

Preferred embodiments of the invention are the compounds of formula I, according to the above, wherein $R^1$ represents a partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms, an aryl or a heteroaryl, all of which may be substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkylthio, $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl, aryl, heteroaryl, wherein aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, or $C_{1-6}$-alkoxy; $NR^8R^9$, wherein $R^8$ and $R^9$ independently represent hydrogen, $C_{1-6}$-alkyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, or $R^8$ and $R^9$ together form a ring which may optionally contain further nitrogen, oxygen or sulfur atoms and which may be partly saturated;

p is 0, 1, 2 , 3 or 4;

$R^2$ represents hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$-alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

$R^3$, $R^6$ and $R^7$ independently represent hydrogen or $C_{1-6}$-alkyl;

**A** and **B** independently represent $-(CH_2)_nX(CH_2)_m-$, wherein X represents $-CR^4R^5$, O or S, wherein $R^4$ and $R^5$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; n is 0-12 and m is 0-12 with the proviso that $1 \leq n+m \leq 12$ and when X represents O or S then $n \geq 2$ and $m \geq 2$;

**D** represents hydrogen or $C_{1-6}$-alkyl, or a pharmaceutically acceptable addition salt thereof;

with the proviso that the compound is not N-[8-[(3-aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide, N-[3-[(8-aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide or N-[4-[(3-aminopropyl)amino]butyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide;

Preferred embodiments of the invention are the compounds according to formula I as above, wherein $R^2$ represents $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$ alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

Preferred embodiments of the invention are the compounds according to formula I according to the above, wherein $R^1$ represents an optionally substituted aryl or heteroaryl;

Preferred embodiments of the invention are the compounds according to any of the above, wherein D represents hydrogen or $C_{1-6}$-alkyl;

Preferred embodiments of the invention are the compound according to any of the above wherein A represents $-(CH_2)_nCH_2(CH_2)_m-$ and $3 \leq n + m \leq 8$; in a more preferred embodiment of the invention n + m is 7;

Preferred embodiments of the invention are the compounds according to any of the above wherein p is 1;

Preferred embodiments of the invention are the compounds according to any of the above wherein B represents $-(CH_2)_nCH_2(CH_2)_m-$ and $1 \leq n + m \leq 6$; in a more preferred embodiment of the invention n + m is 2;

Preferred embodiments of the invention are the compounds according to any of the above wherein A and B together represent carbon chains consisting of at least 8 carbon atoms.

In a more preferred embodiment of the invention, A and B together represent carbon chains consisting of at least 10 carbon atoms.

In a more preferred embodiment of the invention, A and B together represent carbon chains consisting of 11 carbon atoms.

In a preferred embodiment of the invention, D represents hydrogen or $C_{1-6}$-alkyl;

In the most preferred embodiment of the invention, the compounds according to the invention are the following:

**2i**, (*S*)-*N*-[7-[4-Aminobutyl)amino]heptyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2j**, (*S*)-*N*-[6-[5-Aminopentyl)amino]hexyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2k**, (*S*)-*N*-[4-[7-Aminoheptyl)amino]butyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2l**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenylmethyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2m**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-2-ethyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2n**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-3-propyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2o**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-3-prop-2-enyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2p**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-2-yl-1-oxometyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2q**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-3-yl-1-oxomethyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2r**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-4-yl-1-oxomethyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2s**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxo-cyclohexylmethyl)amino]benzenepropaneamide bis(trifluoroacetate),

**2t**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxoethyl)amino]benzenepropaneamide bis(trifluoroacetate),
**2u**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxopropyl)amino]benzenepropaneamide bis(trifluoroacetate),
**2v**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxohexyl)amino]benzenepropaneamide bis(trifluoroacetate) or
**2x**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxo-3-dimethylbutyl)amino]benzenepropaneamide bis(trifluoroacetate)
or a pharmaceutically acceptable salt thereof.

Diseases responsive to the AMPA receptor are caused by excessive stimulation of the excitatory amino acid receptor, which leads to neuronal cell damage or loss of neurons by excitotoxicity. Such excitotoxicity has been implicated in both acute and chronic CNS conditions. Diseases responsive to AMPA receptor antagonists are stroke, cerebral ischemia, spinal cord trauma, head trauma, Parkinson's disease, tardive dyskinesia, Alzheimer's Disease, Huntington's chorea, AIDS encephalopathy, amyotrophic lateral sclerosis, epilepsy, convulsion, spasms, hypoxia, hypoglycemic neuronal damage, ocular damage, migraine headache, psychosis, pain, anxiety, emesis, retinal neuropathy and tinnitus.

Pharmaceutically acceptable addition salts are those which form pharmacological acceptable anions such as maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The compounds of the invention may be administered in any suitable way such as orally or parenterally, and it may be presented in any suitable form for such administration, for example

in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine.

Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g. by fractional crystallisation of d- or l- (tartrates, mandelates or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

**Definition of Substituents**

Halogen means fluoro, chloro, bromo or iodo.

The term $C_{1-6}$-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, $C_{2-6}$-alkenyl and $C_{2-6}$-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond, respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The term $C_{3-8}$-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl designates a cycloalkyl as defined above and an alkyl as above.

The terms $C_{1-6}$-alkoxy and $C_{1-6}$-alkylthio designate such groups in which the alkyl group is $C_{1-6}$-alkyl as defined above.

The terms $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl and $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl designate such alkyl groups as above substituted at any position with an alkoxygroups or alkylthio as defined above.

The term aryl designates an aromatic hydrocarbon such as phenyl or naphtyl.

The term heteroaryl refers to a mono- or bicyclic heterocyclic aromatic group containing at least one N, S or O atom such as furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrimidyl, tetrazolyl, benzofuranyl, benzothienyl, benzimidazolyl, indolyl, isobenzofuranyl, quinolinyl, benzoxazolyl, isobenzoxazolyl, benzothiazolyl, etc.

A partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms designates groups such as piperidinyl, piperazinyl, tetrahydropyridinyl, morpholinyl, tetrahydrofuryl, tetrahydrothieno, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, etc.

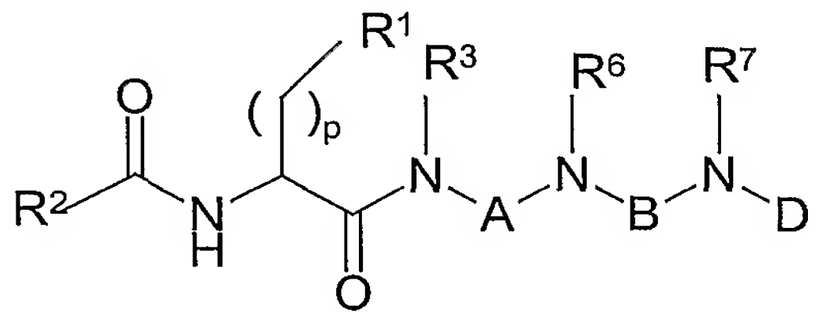
The terms aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl and heteroaryl-$C_{2-6}$ alkenyl, designate alkyl or alkenyl, as defined above, substituted at any position with an aryl or heteroaryl group, as defined above.

The term acyl designates formyl and –CO-$C_{1-6}$ alkyl, wherein alkyl is as defined above.

**Preparatory Examples**

The compounds of the invention may be prepared as follows:

1. Deprotection of the primary and/or secondary amino groups in a compound of the general formula I

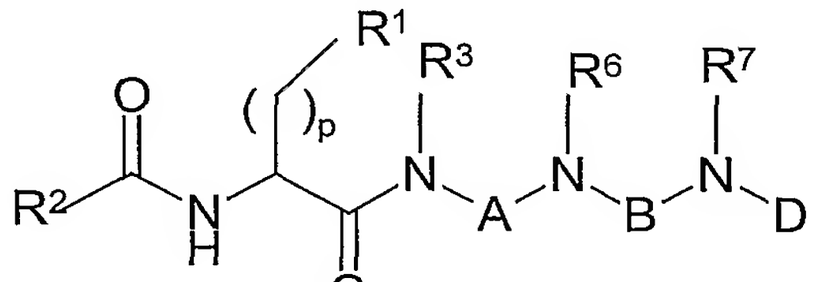


**I**

wherein at least one of the groups $R^6$-$R^9$ are a protecting group such as a group of formula COOR', wherein R' is a allyl, alkyl, benzyl, 4-methoxybenzyl or a *t*-butyl group, or the

protective group is a 2-nitro- or 4-nitrobenzensulfonyl group or it is an allyl group, and the remaining groups are as defined above.

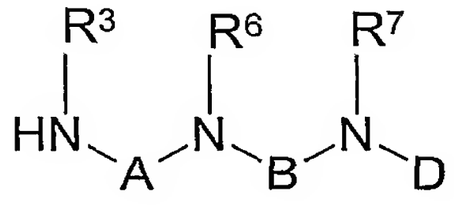
2. Cleaving a polymer bound derivative of formula I and optionally, simultaneously, deprotecting the secondary and/or primary amino groups, and the functional groups in $R^2$,



**I**

wherein $R^7$ or $R^8$ is a functionalised polymer such as a substituted trityl resin or a polymer supported carbamate resin, optionally one or more of the groups $R^6$-$R^9$ are protecting groups such as a group of formula COOR', wherein R' is a 4-methoxybenzyl or *t*-butyl group; $R^1$ is as defined above with reactive functional groups properly protected and the remaining groups are as defined above;

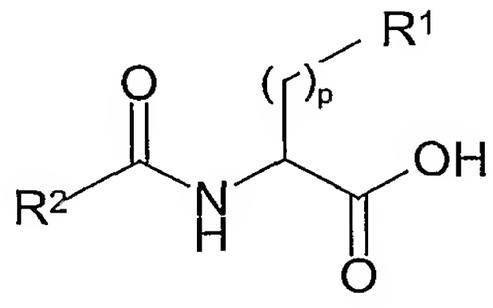
3. Reacting a compound of the formula **II**



**II**

wherein $R^3$, $R^6$, $R^7$, A, B, and D are as defined above,

with a compound of the formula **III**

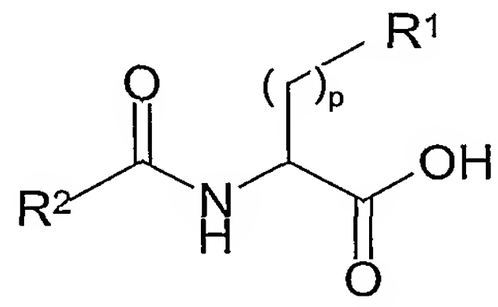


**III**

wherein p, $R^1$ and $R^2$ are as defined above.

In method 1, 2-nitrobenzenesulfonyl groups are cleaved using 2-mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) according to literature procedures (Miller and Scanlan, *J. Am. Chem. Soc.* **1997**, *119*, 2301-02). Carbamate protected amino groups are deprotected by methods obvious to the chemist skilled in the art.

The compounds of formula I used as starting material for method 1 is prepared by coupling of properly protected polyamines with compounds of formula **IV**:



**IV**

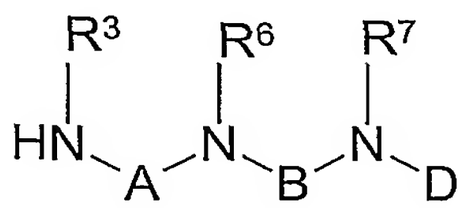
wherein p, $R^1$ are as defined above with reactive functional groups properly protected and $R^2$ is as defined above, using standard coupling conditions such as dicyclohexylcarbodiimide (DCC).

The compounds of formula **IV** are prepared according to literature procedures (Strømgaard et al. *J. Med. Chem.* **1999**, *42*, 5224-34). Properly protected polyamines are prepared by methods obvious to the chemist skilled in the art and according to the procedures outlined in the examples. 8-[[3-[[(2-Nitrophenyl)sulfonyl]amino]propyl]amino]octylamine is prepared as follows: Conjugate addition of 1,8-octanediamine to acrylonitrile afford 3-[(8-aminooctyl)amino]propanenitrile. The amino groups are protected using di(*tert*-butyl) dicarbonate, prior to reduction of the nitrile group using Raney nickel resulting in the di-BOC derivative of *N*-(3-aminopropyl)-1,8-octanediamine. The primary amino group of this polyamine is protected using 2-nitrobenezenesulfonyl chloride, followed by removal of the BOC groups with TFA to give the desired product.

The cleavage and optional, simultaneous deprotection in method 2 is performed using acidic condition such as TFA in an organic solvent preferably dichloromethane using appropriate

scavenger reagents such as water or triisopropylsilane.

The compounds of formula I used as starting material for the general method 2 is prepared by reacting a properly protected polymer bound polyamine of formula V with a properly protected substituted α-amino acid using excess of HATU and collidine as coupling reagents.



**V**

In the above formula **V**, either $R^7$ or $R^8$ is a functionalised polymer such as a substituted trityl resin or a polymer supported carbamate resin, optionally, one or more of the groups $R^6$-$R^9$ are protecting groups such as a group of formula COOR', wherein R' is a 4-methoxybenzyl or *t*-butyl group, and the remaining groups are as defined above. Generally, the amino group in the α-amino acid is protected with a Fmoc group and functional groups in the $R^1$ are protected by protecting groups known from the area of peptide synthesis. Deprotection of the primary amino group is carried out with piperidine, and in the subsequent step, the *N*-acyl group is introduced using acids of formula $R^2COOH$ and HATU and collidine as coupling reagents. The solid phase reaction sequence outlined has been shown to result in final products of high optical purity if optical pure α-amino acids are used as starting materials (Strømgaard et al. *Chirality* **2000**, *12*, 93-102).

The properly protected substituted α-amino acids are commercially available or prepared by conventional methods.

The resin bound polyamines of formula **V** are prepared by linking properly protected polyamines to the resin according to literature methods (Strømgaard et al. *Chirality* **2000**, *12*, 93-102). Alternatively, the resin bound polyamines are prepared in a sequential manner according to literature procedures (Wang et al. *Org. Lett.* **2000**, *2*, 1581-83, Chhabra et al. *Tetrahedron Lett.* **2000**, *41*, 1099-1102).

**Experimental Section**

NMR spectra were recorded on a Varian Gemini 2000 spectrometer, a Bruker AMX 400 spectrometer or a Bruker Avance DRX 500 spectrometer, operating for $^1H$ at 300.07, 400.13 and 500.13 MHz, respectively, using tetramethylsilane (TMS) or sodium 4,4-dimethyl-4-silapentanesulfonate (DSS) as internal standard for organic solvents and $D_2O$ solutions, respectively. Coupling constants ($^nJ$) are expressed as numeric values in Hz. Accurate mass measurements (± 5 ppm) were performed at the Department of Chemistry, University of Odense, Odense, Denmark, on a Kratos MS50RF mass spectrometer equipped with a FAB source, using glycerol as matrix or on a IonSpec Fourier Transformer Mass Spectrometer, using Matrix Assisted Laser Desorption Ionization (MALDI) with 2,5-dihydroxybenzoic acid as matrix. Analytical and preparative high performance liquid chromatography – mass spectrometry (HPLC-MS) was performed on a Perkin Elmer API 150EX instrument equipped with Turbo Ionspray (electronspray ionisation) source. The HPLC system consisted of two Shimadzu LC8A pumps. UV trace was obtained with a Shimadzu SPD10A detector operating at 274 nm. Evaporating light scattering (ELS) trace was obtained with an Eurosep DDL 31 Light Scattering Detector, and was used for determination of chemical purity of synthetic intermediates and final products. Analytical HPLC-MS was performed on a 50 x 4.6 mm YMC RP18 column with 2 mL/min of $H_2O/CH_3CN/CF_3COOH$ (90:10:0.05), raising during 7 min to 10:90:0.05. Preparative HPLC-MS (split-flow MS detection) was performed on the same stationary phase with a 50 x 20 mm column and the same solvent gradient at 22.7 mL/min, injecting about 10 mg of material per run.

Melting points were determined in capillary tubes and are uncorrected.

**Examples**

## Preparation of intermediates

3-[(8-Aminooctyl)amino]propanenitrile

Acrylonitrile (3.16 mL, 48.00 mmol) was added to a solution of 1,8-octanediamine (5.77 g, 40.0 mmol) in MeOH (15 mL) at 0 °C, and the reaction mixture was stirred for 16 h, protected from light. The solvent was evaporated *in vacuo*, and the residue purified by flash chromatography ($CH_2Cl_2$, then $CH_2Cl_2$/MeOH 100:1) to give 3-[(8-

aminooctyl)amino]propanenitrile as a clear oil (4.42 g, 56%). $^1$H NMR (300 MHz, $CDCl_3$): δ 1.23-1.29 (m, 3'-, 4'-, 5'- and 6'-$CH_2$), 1.33-1.48 (m, 2'- and 7'-$CH_2$), 2.47 (t, 2 H, $^3J = 6.6$), 2.57 (t, 2 H, $^3J = 7.5$), 2.63 (t, 2 H, $^3J = 6.0$) and 2.88 (t, 2 H, $^3J = 6.9$) (2-, 3-, 1' and 8'-$CH_2$). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 18.5, 26.6, 27.0, 29.2, 29.3, 29.8, 33.6, 42.1, 45.0, 49.1, 118.8. MS (ES): 198 (M+1).

(2-Cyanoethyl)[8-[[(1,1-dimethylethoxy)carbonyl]amino]octyl]carbamic acid 1,1-dimethyl ester

3-[(8-aminooctyl)amino]propanenitrile (2.210 g, 11.20 mmol) was dissolved in $CH_2Cl_2$ (40 mL) and di-*tert*-butyl dicarbonate (4.840 g, 22.18 mmol) was added. After 16 h the reaction mixture was poured into water and extracted with EtOAc (3 x 40 mL). The combined organic extracts were successively washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl. The organic phase was dried ($MgSO_4$), concentrated *in vacuo*, the residue dissolved in a 1:1 mixture of MeOH and 0.5 N NaOH added and the solution stirred for 1 h. The solvent was removed by evaporation, the residue dissolved in $CH_2Cl_2$ (100 mL), the solution washed with water (2 x 100 mL) and saturated aq. NaCl (2 x 100 mL), dried ($MgSO_4$) and evaporated, to give the title compound as a clear oil (2.82 g, 64%), which was used without further purification. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.30 (m, 3'-, 4'-, 5'- and 6'-$CH_2$), 1.42-1.56 [m, 2'- and 7'-$CH_2$ and 2 x $C(CH_3)_3$], 2.60 (m, 2 H), 3.10 (m, 2 H), 3.25 (t, 2 H, $^3J = 7.8$) and 3.46 (t, 2 H, $^3J = 6.6$) (2-, 3-, 1' and 8'-$CH_2$). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 17.1, 26.7, 26.8, 28.4 (3 C), 28.5 (3 C), 29.3 (2 C), 30.1 (3 C), 40.8, 43.9, 48.6, 79.1, 80.5, 118.6, 156.3 (2 C). MS (ES): 398 (M+1).

(3-Aminopropyl)[8-[[(1,1-dimethylethoxy)carbonyl]amino]octyl]carbamic acid 1,1-dimethyl ester

Raney nickel (0.600 g) was added to a solution of the (2-cyanoethyl)[8-[[(1,1-dimethylethoxy)carbonyl]amino]octyl]carbamic acid 1,1-dimethyl ester (2.400 g, 6.04 mmol) and NaOH (0.600 g, 15.09 mmol) in EtOH (96%, 30 mL). The suspension was hydrogenated under 40 psi at room temperature for 28 h. The mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The residue was taken up in water (100 mL) and the product

extracted with $CH_2Cl_2$ (4 x 30 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a pale oil (1.900 g, 78%) which was used without further purification. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.29 (m, 3-, 4-, 5- and 6-$CH_2$), 1.44-1.45 [m, 2- and 7-$CH_2$ and 2 x $C(CH_3)_3$], 1.66 (p, 2'-$CH_2$), 2.70 (t, 2 H, $^3J$ = 6.9) and 3.053.32 (m, 6 H) (1-, 8-, 1'- and 3'-$CH_2$). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 26.7, 26.8, 26.9, 28.4, 28.5 (3 C), 28.6 (3 C), 29.3, 29.4, 30.1, 40.7, 43.9, 47.0, 48.7, 79.1, 79.3, 155.2, 156.3. MS (ES): 402 (M+1), 302 [(M+1) – $(CH_3)_2C=CH_2$ – $CO_2$].

[3-[[(2-Nitrophenyl)sulfonyl]amino]propyl][8-[[(1,1-dimethylethoxy)carbonyl]amino]octyl]carbamic acid 1,1-dimethyl ester

2-Nitrobenzenesulfonyl chloride (0.426 g, 1.92 mmol) in $CH_2Cl_2$ (5 mL) was added slowly to (3-aminopropyl)[8-[[(1,1-dimethylethoxy)carbonyl]amino]octyl]carbamic acid 1,1-dimethyl ester (0.644 g, 1.60 mmol) dissolved in $CH_2Cl_2$ (20 mL). The solution was cooled to 0 °C, pyridine (0.182 mL, 2.25 mmol) added and the reaction mixture stirred at 0 °C for 1 h, followed by 1 h at room temperature. The solvent was removed *in vacuo* and the crude product purified by flash chromatography (EtOAc/heptane 1:2 and then 1:1), to give the title compound as a slightly yellow oil (0.660 g, 70%). $^1$H NMR (500 MHz, $CD_3OD$): δ 1.22-1.33 (m, 3-, 4-, 5- and 6-$CH_2$), 1.42 [m, 2 x $C(CH_3)_3$], 1.44-1.50 (m, 2- and 7-$CH_2$), 1.71 (m, 2'-$CH_2$), 3.01 (t, 2 H, $^3J$ = 7.1), 3.04 (t, 2 H, $^3J$ = 7.1), 3.12 (t, 2 H, $^3J$ = 7.5) and 3.21 (t, 2 H, $^3J$ = 7.1) (1-, 8-, 1'- and 3'-$CH_2$), 7.80-7.82 (m, 2 H), 7.84-7.86 (m, 1 H) and 8.05-8.09 (m, 1 H) (aromatic H). $^{13}$C NMR (125.8 MHz, $CD_3OD$): δ 40.0, 40.3, 43.7, 78.1, 79.3, 124.2, 129.9, 131.9, 133.2, 133.3, 148.0, 155.7, 156.9, remaining signals at 26.1-29.3. MS (ES): 587 (M+1), 487 [(M+1) – $(CH_3)_2C=CH_2$ – $CO_2$], 387 [(M+1) - 2$(CH_3)_2C=CH_2$ – 2$CO_2$].

8-[[3-[[(2-Nitrophenyl)sulfonyl]amino]propyl]amino]octylamine

[3-[[(2-Nitrophenyl)sulfonyl]amino]propyl][8-[[(1,1-dimethylethoxy)carbonyl]amino]octyl]carbamic acid 1,1-dimethyl ester (0.660 g, 1.13 mmol) was dissolved in $CH_2Cl_2$ (20 mL), TFA (0.9 mL, 11.5 mmol) added, and the reaction mixture stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography [MeOH/$CH_2Cl_2$/$(CH_3)_2CHNH_2$ 20:20:1 and then 10:10:1] to give the title compound as a clear oil (0.402 g, 92%). $^1$H NMR (500 MHz,

$CD_3OD$): δ 1.34 (m, 3-, 4-, 5- and 6-$CH_2$), 1.48 (m, 4 H) and 1.69 (p, 2 H) (2-, 7- and 2'-$CH_2$), 2.52 (t, 2 H, $^3J = 7.5$),
2.61 (p, 2 H, $^3J = 7.1$), 2.64 (t, 2 H, $^3J = 7.1$) and 3.09 (t, 2 H, $^3J = 6.6$) (1-, 8-, 1' and 3'-$CH_2$), 7.78-7.81 (m, 2 H), 7.82-7.85 (m, 1 H) and 8.06-8.09 (m, 1 H) (aromatic H). $^{13}C$ NMR (125.8 MHz, $CD_3OD$): δ 28.2, 28.6, 30.5, 30.6, 30.8, 30.9, 33.7, 42.7, 43.0, 48.1, 50.9, 126.1, 131.8, 133.8, 135.1, 135.5, 150.0. MS (ES): 387 (M+1).

*N′*,*N′′′′*-Bis(trifluoroacetyl)spermine Bis(trifluoroacetate)

To a solution of spermine (4.05 g, 20.0 mmol) in $CH_3CN$ (60 mL), ethyl trifluoroacetate (11.9 mL, 100 mmol) and $H_2O$ (0.72 mL, 40.0 mmol) were added, and the mixture was boiled under reflux for 3 h. The reaction mixture was allowed to cool to room temperature, $CH_2Cl_2$ (20 mL) added, and the white precipitate formed was filtered off, washed thoroughly with $CH_2Cl_2$, and dried *in vacuo* overnight. Yield 11.22 g (90%). Mp 199-200 °C, lit. mp. 195-198 °C (O'Sullivan and Dalrymple *Tetrahedron Lett* **1995**, *36*, 3451-3452) $^1H$ NMR [$(CD_3)_2SO$)] δ 1.61 (broad s, 6- and 7-$CH_2$), 1.82 (apparent q, 2- and 10-$CH_2$), 2.92 (m, 3-, 5-, 8- and 10-$CH_2$), 3.26 (apparent q, 1- and 12-$CH_2$), 8.59 (broad s, NH), 9.59 (broad s, CONH); $^{13}C$ NMR [$(CD_3)_2SO$)] δ 22.8 (6- and 7-C), 25.2 (2- and 11-C), 36.7 (1- and 12-C), 44.5 and 46.2 (3-, 5-, 8- and 10-C), 116.0 (q, $^1J_{CF} = 287.5$, $CF_3$), 117.3 (q, $^1J_{CF} = 336.0$, counterion $CF_3$), 156.6 (q, $^2J_{CF} = 36.1$, $\underline{C}OCF_3$), 158.7 (q, $^2J_{CF} = 31.3$, counterion $\underline{C}OCF_3$); MS m/z 395.2 (M + 1); ELS 99.2

*N′*,*N′′′′*-Bis(trifluoroacetyl)-*N′′*,*N′′′*-bis(*tert*-butoxycarbonyl)spermine

A suspension of *N′*,*N′′′′*-Bis(trifluoroacetyl)spermine Bis(trifluoroacetate) (8.82 g, 14.17 mmol) in $Et_3N$ (50 mL) was cooled to 0 °C, and a solution of di(*tert*-butyl) dicarbonate (6.19 g, 28.3 mmol) in dry THF (15 mL) was added. The reaction mixture was stirred for 3 h while warming to room temperature, $H_2O$ (150 mL) was added and the mixture extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with $H_2O$ (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellowish oil which was crystallised from $Et_2O$ (45 mL) to give white crystals (7.88 g, 93%). Mp 104-105 °C, lit. mp. 93.5-95 °C (O'Sullivan et al. *Bioorg. Med. Chem.* **1997**, *5*, 2145-2155); $^1H$ NMR ($CDCl_3$) δ 1.46 [s, 2 x $C(CH_3)_3$], 1.50 (broad s, 6- and 7-$CH_2$), 1.71 (broad s, 2- and 11-$CH_2$), 3.15 (broad s, 1- and 12-$CH_2$),

3.32 (m, 3-, 5-, 8- and 10-$CH_2$); $^{13}$C NMR ($CDCl_3$) δ 25.8 (6- and 7-C), 27.1 (2- and 11-C), 28.2 ($CH_3$), 35.7 (1- and 12-C), 42.9 and 46.7 (3-, 5-, 8- and 10-C), 80.3 [$\underline{C}(CH_3)_3$], 116.0 ($^1J_{CF}$ = 288.3 Hz, $CF_3$), 157.1 (CO), 157.4 ($^2J_{CF}$ = 36.1, $\underline{C}OCF_3$); MS m/z 595.5 (M + 1), 495.5 [(M+1) – $(CH_3)_2C{=}CH_2$ - $CO_2$], 395.5 [(M+1) - 2$(CH_3)_2C{=}CH_2$ - 2$CO_2$]; ELS 99.2%.

*N′′,N′′′*-Bis(*tert*-butoxycarbonyl)spermine

A solution of *N′,N′′′′*-Bis(trifluoroacetyl)-*N′′,N′′′*-bis(*tert*-butoxycarbonyl)spermine (7.77 g, 13.1 mmol) in MeOH (250 mL) was cooled to 5 °C, 0.2 M aq. NaOH (144 mL, 28.8 mmol) added, and the solution left overnight at room temperature. MeOH was removed *in vacuo*, and the remaining aq. solution was extracted with $CH_2Cl_2$/MeOH (9:1, 6 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (O'Sulivan et al. *Bioorg. Med. Chem.* **1997**, *5*, 2145-2155) (2.89 g, 55%), which was used without further purification. $^1$H NMR ($CDCl_3$) δ 1.45 [broad s, $C(CH_3)_3$], 1.50 (broad s, 6- and 7-$CH_2$), 1.64 (apparent p, 2- and 11-$CH_2$), 2.69 (m, 1- and 12-$CH_2$), 3.16-3.28 (m, 3-, 5-, 8- and 10-$CH_2$); $^{13}$C NMR ($CDCl_3$) δ 25.3 and 25.7 (6- and 7-C), 28.2 ($CH_3$) 31.7 and 32.4 (2- and 11-C), 38.9 and 39.2 (1- and 12-C), 43.7, 44.1, 46.2 and 46.5 (3-, 5-, 8- and 10-C), 79.0 [$\underline{C}(CH_3)_3$], 155.4 (CO); MS m/z 403.6 (M + 1) 303.6 [(M+1) - $(CH_3)_2C{=}CH_2$ - $CO_2$], 203.4 [(M+1) - 2$(CH_3)_2C{=}CH_2$ - 2$CO_2$]; ELS 99.4%.

Preparation of *N*-Phtalimido alcohols, general synthetic procedure

A solution of a bromo alcohol (19.9 mmol) and potassium phtalimide (23.8 mmol) in DMF (10 mL) was refluxed overnight. The reaction was cooled and evaporated to dryness. The crude product was stirred for 20 min in $CHCl_3$ (50 mL) and filtered. The filtrate was washed once with water and dried ($MgSO_4$). The product was used without further purification.

**The following compounds were prepared according to the general procedure.**

7-Phtalimido heptanol

Yield: 91%. $^1$H NMR ($CDCl_3$): $\delta$ 1.35 (bs, 8H), 1.48–1.74 (m, 2H), 3.63 (t, $J$ = 6.5 Hz, 2H), 3,68 (t, $J$ = 7.0 Hz, 2H), 7.68 (dd, $J$ = 8.0 Hz, $J$ = 1.0 Hz, 2H), 7.82 (dd, $J$ = 8.0 Hz, $J$ = 1.0 Hz, 2H).

8-Phtalimido octanol

Yield: 91%. $^1$H NMR ($CDCl_3$): $\delta$ 1.34 (bs, 8H), 1.54–1.57 (m, 2H), 1.66–1.69 (m, 2H), 3.63 (, $J$ = 6.0 Hz, 2H), 3.69 (t, $J$ = 7.0 Hz, 2H), 7.71 (dd, $J$ = 8.2 Hz, $J$ = 1.0 Hz, 2H), 7.84 (dd, $J$ = 8.2 Hz, $J$ = 1.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 26.0, 27.1, 28.9, 29.4, 29.6, 33.1, 38.4, 63.4, 123.5, 132.6, 134.2, 168.8.

9-Phtalimido nonanol

Yield: 87%. $^1$H NMR ($CDCl_3$): $\delta$ 1.31 (bs, 10H), 1.53–1.70 (m, 4H), 3.63 (t, $J$ = 7.8 Hz, 2H), 3.68 (t, $J$ = 7.5 Hz, 2H), 7.71 (dd, $J$ = 7.8 Hz, $J$ = 1.0 Hz, 2H), 8.84 (dd, $J$ = 7.8 Hz, $J$ = 1.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 25.5, 26.7, 28.4, 28.9, 29.1, 29.2, 32.6, 37.9, 62.9, 123.0, 132.1, 133.7, 168.3.

Preparation of Amino alcohols, general synthetic procedure

To a solution of a phtalimido alcohol (30.1 mmol) in ethanol (300 mL) was added hydrazine hydrate (150 mmol) and the reaction was stirred under reflux for 20 h. The mixture was cooled, filtered and washed with ice cold ethanol. Evaporation *in vacuo* gave an yellow oil that was suspended in $CHCl_3$ (80 mL), washed with 1M NaOH (2 x 50 mL) and water (2 x 50 mL) and dried ($MgSO_4$). The product was used without further purification.

**The following compounds were prepared according to the general procedure**

7-Amino heptanol

Yield: 33%. $^1$H NMR ($CDCl_3$): $\delta$ 1.20–1.52 (m, 10H), 1.58 (t, $J$ = 6.0 Hz, 2H), 2.69 (t, $J$ = 7.0 Hz, 2H), 3.64 (t, $J$ = 6.5 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 26.1, 27.2, 29.6, 33.2, 42.6, 63.3, 71.2.

8-Amino octanol

Yield: 45%. $^1$H NMR ($CDCl_3$): $\delta$ 1.32 (s, 10H), 1.44 (t, $J$ = 6.6 Hz, 2H), 1.55 (t, $J$ = 6.9 Hz, 2H), 1.62 (bs, 2H), 2.67 (t, $J$ = 7.2 Hz, 2H), 3.60 (t, $J$ = 6.7 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 26.1, 27.2, 29.8, 29.8, 33.2, 34.1, 42.6, 63.0.

9-Amino nonanol

Yield: 77%. $^1$H NMR ($CDCl_3$): $\delta$ 1.31–1.46 (m, 12H), 1.56 (t, $J$ = 6.8 Hz, 2H), 2.67 (t, $J$ = 6.8 Hz, 2H), 3.63 (t, $J$ = 6.5 Hz, 2H). $^{13}$C NMR ($CDCl_3/CD_3OD$): $\delta$ 30.3, 31.3, 33.8, 33.9, 34.0, 36.5, 37.1, 45.7, 66.9.

Preparation of N-(Trimethylsilyl)ethoxycarbonyl amino alcohols, general synthetic procedure

To a solution of an amino alcohol (42.7 mmol) in $CH_2Cl_2$ (70 mL) was added triethylamine (85.4 mmol) and a solution of 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (42.7 mmol) in $CH_2Cl_2$ (20 mL). The reaction was left overnight at room temperature and evaporated. The resulting yellow oil was redissolved in $CH_2Cl_2$ and washed several times with brine, saturated $NaHCO_3$ and 2M NaOH until the organic phase was colourless. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a clear oil. The product was used without further purification.

**The following compounds were prepared according to the general procedure**

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]ethanol

Yield: 92%. $^1$H NMR ($CDCl_3$): $\delta$ 0.10 (s, 9H), 0.94 (t, $J$ = 8.3 Hz, 2H), 2.97 (bs, 1H), 3.29 (m, 2H), 3.66 (t, $J$ = 5.3 Hz, 2H), 4.12 (t, $J$ = 8.5 Hz, 2H), 5.25 (bs, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ -1.7, 17.6, 43.2, 62.1, 63.1, 157.5.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]propanol

Yield: 89%. $^1$H NMR ($CDCl_3$ ): $\delta$ 0.16 [s, $Si(CH_3)_3$ ], 0.98 (t, $J$ =8.3 Hz, $SiCH_2$ ), 1.70 (m, $CH_2$), 2.70 (br s, OH/NH), 3.33 (q, $J$ =6.0 Hz, NH-$CH_2$ ), 3.68 (q, $J$ = 5.6 Hz, HO-$CH_2$ ), 4.18 (t, $J$ = 8.4 Hz, OCO-$CH_2$), 4.89 (br s, OH/NH).75 $^{13}$C NMR ($CDCl_3$ ): $\delta$ –1.6 (3C), 17.7, 32.7, 37.3, 59.3, 63.2, 156.5.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]butanol

Yield: 90%. $^1$H NMR ($CDCl_3$ ): δ 0.15 [s, $Si(CH_3)_3$ ], 0.97 (t, $J$=8.2 Hz, $SiCH_2$ ), 1.60 (m, 2H, $CH_2$ ), 3.20 (t, $J$ = 7.5 Hz, NH-$CH_2$ ), 3.67 (q, $J$ = 5.1 Hz, HO-$CH_2$ ), 4.15 (t, $J$ = 8.2 Hz, OCO-$CH_2$ ), 4.72 (br s, OH). $^{13}$C NMR ($CDCl_3$ ): δ –1.6 (3C), 17.7, 26.5, 29.6, 40.5, 62.4, 62.8,
156.8.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]pentanol

Yield: 87%. $^1$H NMR ($CDCl_3$): $\delta$ 0.10 (s, 9H), 0.93 (t, $J$ = 8.5 Hz, 2H), 1.34–1.58 (m, 6H), 1.89 (bs, 1H), 3.14 (m, 2H), 3.60 (bs, 2H), 4.10 (t, $J$ = 8.3 Hz, 2H), 4.71 (bs, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ -1.2, 18.1, 23.3, 30.1, 32.5, 41.1, 62.6, 63.1.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]hexanol

Yield: 81%. $^1$H NMR ($CDCl_3$): $\delta$ 0.10 (s, 9H), 0.93 (t, $J$ = 8.5 Hz, 2H), 1.34 (bs, 6H), 1.41–1.56 (m, 4H), 1.94 (bs, 1H), 3.09–3.14 (m, 2H), 3.59 (t, $J$ = 7.8 Hz, 2H), 4.10 (t, $J$ = 8.3 Hz, 2H), 4.69 (bs, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ -1.1, 18.1, 25.7, 26.8, 30.4, 32.9, 41.1, 63.0, 63.2, 157.3.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]heptanol

Yield: 38 %. $^1$H NMR ($CDCl_3$): $\delta$ 0.06 (s, 9H), 0.87 (t, $J$ = 8.5 Hz, 2H), 1.18–1.48 (m, 12H), 1.68 (bs, 1H), 3.0.6–3.11 (m, 2H), 3.58 (t, $J$ = 8.5 Hz, 2H), 4.16 (t, $J$ = 7.3 Hz, 2H), 4.64 (bs, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ -1.6, 17.6, 25.5, 26.5, 28.8, 29.8, 32.5, 62.6, 70.7, 156.7.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]octanol

Yield: 86%. $^1$H NMR ($CDCl_3$): $\delta$ -0.10 (s, 9H), 0.93 (t, $J$ = 8.1 Hz, 2H), 1.28 (s, 8H), 1.45 (t, $J$ = 6.4 Hz, 2H), 1.52 (t, $J$ = 7.2 Hz, 2H), 3.11 (d, $J$ = 6.2, 2H), 3.59 (t, $J$ = 6.6 Hz, 2H), 4.11 (t, $J$ = 8.1 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ -1.6, 17.8, 25.5, 26.5, 29.2, 29.3, 30.0, 32.7, 40.9, 62.9.

3-[*N*-[2-(Trimethylsilyl)ethoxycarbonyl]amino]nonanol

Yield: 48%. $^1$H NMR ($CDCl_3$): $\delta$0.10 (s, 9H), 0.93 (t, $J$ = 8.3 Hz, 2H), 1.26 (s, 10H), 1.44–1.55 (m, 4H), 1.89 (bs, 1H), 3.11 (m, 2H), 3.59 (t, $J$ = 6.5 Hz, 2H), 4.10 (t, $J$ = 8.5 Hz, 2H), 4.70 (bs, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$-2.2, 17.1, 25.0, 26.0, 28.5, 28.6, 28.8, 29.3, 30.1, 40.2, 62.2, 156.2.

**Preparation of the Compounds of the Invention**

**Example 1**

1, (*R,S*)-*N*-[8-[(3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide

(*R,S*)-*N*-(1-Oxobutyl)tyrosine (0.173 g, 0.69 mmol) and DCC (0.157 g, 0.76 mmol) were dissolved in DMF (10 mL) and stirred at room temperature for 30 min. The solution was added dropwise to a solution of 8-[[3-[[(2-nitrophenyl)sulfonyl]amino]propyl]amino]octylamine (0.400 g, 1.04 mmol) in DMF (10 mL) and the reaction mixture stirred at room temperature for 16 h. The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography [EtOAc/heptane/$(CH_3)_2CHNH_2$ 5:5:1 and 3:3:1]. Second purification by flash chromatography ($CH_2Cl_2$/MeOH 1:1) gave the 2-nitrobenzenesulfonyl derivative of (*R,S*)-*N*-[8-[(3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide as a pale yellow oil (0.196 g, 46%). $^1$H NMR (500 MHz, $CDCl_3$): δ 0.92 (t), 1.63 (s) and 2.17 (t) (respectively 4-$CH_3$, 3-$CH_2$ and 2-$CH_2$ of the 1-oxobutyl moiety, both $^3J$ = 7.2), 2.82 and 3.01 (each dd, $^2J_{AB}$ = 13.2, $^3J_{AX}$ = 9.4, $^3J_{BX}$ = 5.2, b-$CH_2$), 4.54 (m, a-CH), 6.69 and 7.03 (each 2 H, tyrosine H), 1.17-1.30 (m, 8 H), 1.50 (p, 2 H) and 1.74 (p, 2 H) (2-, 3-, 4-, 5-, 6-, 7- and 11-$CH_2$), 2.75 (t, 2 H, $^3J$ = 6.6), 2.61 (t, 2 H, $^3J$ = 7.1), 2.99 (m, 1 H) and 3.17-3.24 (m, 3 H) (1-, 8-, 10- and 12-$CH_2$), 7.67-7.71 (m, 2 H), 7.79-7.81 (m, 1 H), and 8.08-8.10 (m, 1 H) (sulfonamide aromatic H), 1.04 (m, 2 H). $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 13.5, 18.9, 26.2, 26.5, 28.3, 28.6, 28.7, 28.8, 29.2, 38.3, 39.2, 42.9, 47.8, 49.4, 50.6, 54.9, 115.6 (2 C), 125.0, 127.4, 130.2 (2 C), 130.9, 132.4, 133.3, 133.6, 148.0, 155.8, 170.7, 172.8. MS (ES): 630 (M+1).

For deprotection of the 2-nitrobenzenesulfonyl derivative of (*R,S*)-*N*-[8-[(3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide (0.475 g (0.77 mmol) was dissolved in DMF (50 mL), DBU (0.46 mL, 3.07 mmol) and 2-

mercaptoethanol (0.11 mL, 1.53 mmol) added, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography [$CH_2Cl_2$/MeOH/$(CH_3)_2CHNH_2$] to give a yellow oil (0.159 g) which was further purified by preparative HPLC with TIC detection to give the bis(trifluoroacetate) of (*R,S*)-*N*-[8-[(3-Aminopropyl)amino]octyl]-4-hydroxy-α -[(1-oxobutyl)amino]benzenepropanamide as a clear viscous oil (0.140 g, 28%). The material was 97.8% pure according to HPLC with MS (total ion current) detection.

$^1$H NMR (400 MHz, $CD_3OD$): δ 0.85 (t), 1.54 (s) and 2.15 (t) (respectively 4-$CH_3$, 3-$CH_2$ and 2-$CH_2$ of the 1-oxobutyl moiety, both $^3J = 7.4$), 2.78 and 2.95 (each dd, $^2J_{AB} = 13.8$, $^3J_{AX} = 8.2$, $^3J_{BX} = 7.2$, b-$CH_2$), 4.46 (dd, a-CH), 6.69 and 7.04 (each 2 H, aromatic H), 1.18-1.44 (m, 10 H) and 1.69 (p, 2 H) (2-, 3-, 4-, 5-, 6- and 7-$CH_2$), 2.05 (m, 11-$CH_2$), 2.98-3.18 (m, 1-, 8-, 10- and 12-$CH_2$). $^{13}$C NMR (100.6 MHz, $H_2O/D_2O$ 9:1, pH 7.64): δ 15.3, 21.7, 26.6, 28.1, 28.2, 28.3, 30.5, 30.6 (2 C), 39.1, 39.5, 39.9, 41.9, 47.2, 50.6, 58.3, 118.1 (2 C), 130.8, 133.1 (2 C), 157.1, 175.5, 179.5. HRMS (FAB): $C_{24}H_{42}N_4O_3$ requires M+1 at *m/z* 435.333, found 435.334.

**Example 2.1**

Preparation of resinbound *N′′,N′′′*-Bis(*tert*-butoxycarbonyl)spermine

Trityl chloride resin (0.244 g, 0.50 mmol) was added in five portions to a solution of *N′′,N′′′*-Bis(*tert*-butoxycarbonyl)spermine (2.01 g, 5.0 mmol) in THF (10 mL) and the suspension stirred for 2 h at room temperature. The solvent was removed by filtration and the resin treated with 10% diisopropylethylamine (DIEA) in MeOH (10 mL) for 5 min to cap any remaining chlorine substituents. The resin was then washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL) and dried *in vacuo*. The loading of the resulting resin was 1.17 mmol/g under the assumption that the reaction had proceeded to completion.

General synthetic procedure

A solution of a either (*S*)-*N*-Fmoc-3-(*tert*–butoxy)phenylalanine or (*S*)-*N*-Fmoc-*O*-(*tert*-butyl)tyrosine (1.54 mmol) and HATU (1.54 mmol) in DMF (3 mL), and of collidine (2.32 mmol) in DMF (2 mL) were added to resinbound *N′′,N′′′*-Bis(*tert*-butoxycarbonyl)spermine (0.39 mmol) placed in 10 mL syringes equipped with a polypropylene filter and a stopper. The

syringes were agitated for 2 h at room temperature, the solvent removed, and the resins washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL).

A solution of 20% piperidine in DMF (v/v, 5 mL) was added to each of these resins and the mixtures agitated for 3 min at room temperature. The resins were subsequently washed with DMF (3 x 5 mL), treated with 20% piperidine in DMF (5 mL) for further 20 min and washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL).

A solution of butanoic acid, phenylacetic acid or cyclohexylacetic acid (1.54 mmol) and HATU (1.54 mmol) in DMF (3 mL) was added to each of the above- prepared resins, followed by addition of collidine (2.32 mmol) in DMF (2 mL). The mixtures were agitated for 2 h at room temperature and the resins washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL), to give resinbound *O-tert* butyl protected philanthotoxin analogues.

$TFA/iPr_3SiH/H_2O$ (95:2.5:2.5) (5 mL) was added to each of the above resins, and the mixtures were agitated for 2 h at room temperature. The solvent was removed and the resins washed with

MeOH (2 x 5 mL) and $CH_2Cl_2$ (2 x 5 mL). The combined solvents were concentrated *in vacuo* and triturated with $Et_2O$ to give the crude products which were purified using automated preparative HPLC using split flow MS detection for identification of peaks, giving the products as trifluoroacetates in yields from 53-59%.

**The following compounds were prepared according to the general procedure**

**2a**, (*S*)-*N*-[3-[[4-[(3-Aminopropyl)amino]butyl]amino]propyl]-3-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide tris(trifluoroacetate)

Yield: 57%. $^1$H NMR: δ 0.87 (t), 1.56 (s), 2.18 (t) (respectively 4-$CH_3$, 3-$CH_3$ and 2-$CH_3$ of the 1-oxobutyl moiety, both $^3J = 7.5$), 4.42 (t, α-CH), 6.66 (m, 2 H), 6.71 (m, 1 H) and 7.10 (m, 1 H) (aromatic H), 1.78-1.81 (m, 6 H) and 2.08 (m, 2 H) (2-, 6-, 7- and 11-$CH_2$), 2.84-2.94

(m, 3 H), 2.97-3.02 (m, 3 H), 3.03-3.09 (m, 4 H), 3.13 (t, 2 H, $^3J$ = 8.0) and 3.18-3.30 (m, 2 H) (β-$CH_2$ and remaining $CH_2$ of the polyamine moiety). $^{13}$C NMR: δ 14.0, 20.3, 24.4, 24.5, 25.6, 27.5, 36.8, 38.0, 38.6, 38.7, 46.0, 46.2, 48.2, 48.4, 49.7, 56.8, 114.9, 117.2, 121.4, 130.6, 139.8, 158.7, 175.2, 176.3. HPLC-ELS: 100%. MS (ES): 436.6 (M+1).

**2b**, (*S*)-*N*-[3-[[4-[(3-Aminopropyl)amino]butyl]amino]propyl]-3-hydroxy-α-[(1-oxo-2-phenylethyl)amino]benzenepropanamide tris(trifluoroacetate)

Yield: 53%. $^1$H NMR δ 3.01 (dd, $^2J_{AB}$ = 13.7, $^3J_{BX}$ = 7.1, $H_B$ proton of β-$CH_2$), 3.51 (d) and 3.55 (d) ($^2J$ = 14.1, benzylic H), 4.42 (t, α-CH), 6.65-6.68 (m, 3 H), 7.06-7.10 (m, 1 H), 7.16-7.19 (m, 2 H), 7.20-7.24 (m, 1 H) and 7.25-7.29 (m, 2 H) (aromatic H), 1.70-1.81 (m, 6 H) and 2.07 (p, 2 H) (2-, 6-, 7- and 11-$CH_2$), 2.80-2.92 (m, 5 H), 3.05 (apparent t, 4 H), 3.11 (t, 2 H, $^3J$ = 7.5) and 3.16 (m, 2 H) ($H_A$ proton of β-$CH_2$ and remaining $CH_2$ of the polyamine moiety). $^{13}$C NMR: δ 24.4, 24.4, 25.6, 27.5, 36.8, 38.0, 38.5, 43.5, 46.0, 46.1, 48.2, 48.4, 57.1, 115.0, 117.2, 121.4, 128.0, 129.7 (2 C), 130.3 (2 C), 130.7, 136.7, 139.6, 158.7, 174.2, 175.0. HPLC-ELS: 99.0%. MS (ES): 484.4 (M+1).

**2c**, (*S*)-*N*-[3-[[4-[(3-Aminopropyl)amino]butyl]amino]propyl]-3-hydroxy-α-[(1-oxo-2-cyclohexylethyl)amino]benzenepropanamide tris(trifluoroacetate)

Yield: 54%. $^1$H NMR: δ 4.45 (t, $^3J$ = 7.8, α-CH), 6.64-6.72 (m, 3 H) and 7.10 (m, 1 H) (aromatic H), 0.86-0.89 (m, 2 H), 1.16-1.20 (m, 3 H), 1.47 (m, 1 H) and 1.57-1.65 (m, 5 H) (CH and $CH_2$ of the diamine and the cyclohexylacetyl moiety),1.80 (m, 2-, 6- and 8-$CH_2$), 2.08 (m, 11-$CH_2$ and 2-$CH_2$ of the cyclohexylacetyl moiety), 2.80-3.27 (m, 14H, β-$CH_2$ and the remaining $CH_2$ of the polyamine moiety). $^{13}$C NMR: δ 24.4, 25.5, 27.2, 27.3 (2 C), 27.5, 33.9, 34.2, 36.7, 36.8, 37.9, 38.5, 44.9, 45.9, 46.1, 48.2, 56.7, 114.8, 117.2, 121.3, 130.6, 139.8, 158.6, 175.2, 175.7. HPLC-ELS: 98.7%. MS (ES): 490.5 (M+1).

**2d**, (*S*)-*N*-[3-[[4-[(3-Aminopropyl)amino]butyl]amino]propyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide tris(trifluoroacetate)

Yield: 59%. $^1$H NMR: δ 0.87 (t), 1.55 (s), 2.17 (m) (respectively 4-$CH_3$, 3-$CH_2$ and 2-$CH_2$ of the 1-oxobutyl moiety, both $^3J$ = 7.4), 4.37 (t, $^3J$ = 7.8, α-CH), 6.71 and 7.05 (each 2H,

aromatic H), 1.78 (m, 2-, 6- and 8-$CH_2$), 2.08 (p, 11-$CH_2$), 2.79-3.28 (m, 14H, β-$CH_2$ and the remaining $CH_2$ of the polyamine moiety). $^{13}$C NMR: δ 14.0, 20.3, 24.3, 24.4, 25.5, 27.4, 36.8, 37.9, 37.9, 38.7, 45.9, 46.2, 48.2, 48.3, 57.1, 116.3 (2 C), 128.9, 131.3 (2 C), 157.5, 175.2, 176.3. HPLC-ELS: 99.5%. MS (ES): 435.5 (M+1).

**2e**, (*S*)-*N*-[3-[[4-[(3-Aminopropyl)amino]butyl]amino]propyl]-4-hydroxy-α-[(1-oxo-2-phenylethyl)amino]benzenepropanamide tris(trifluoroacetate)

Yield: 59%. $^1$H NMR: δ 4.36 (t, $^3J$ = 7.8, α-CH), 6.69 (m, 2 H), 7.01 (m, 2 H), 7.17 (m, 2 H) and 7.22-7.28 (m, 3 H) (aromatic H), 1.77 (m, 2-, 6- and 8-$CH_2$), 2.08 (p, 11-$CH_2$), 2.79-3.28 (m, 14H, β-$CH_2$ and the remaining $CH_2$ of the polyamine moiety), 3.49 (d) and 3.54 (d) ($^2J$ = 14.5, benzylic H). $^{13}$C NMR: δ 24.3 (2 C), 25.4, 27.4, 36.8, 37.8, 37.8, 43.5, 45.9, 46.2, 48.1, 48.3, 57.3, 116.4 (2 C), 128.0, 128.7, 129.7 (2 C), 130.2 (2 C), 131.3 (2 C), 136.7, 157.5, 174.2, 175.0. HPLC-ELS: 99.4%. MS (ES): 484.4 (M+1) (Anis et al. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 764-773).

**2f**, (*S*)-*N*-[3-[[4-[(3-Aminopropyl)amino]butyl]amino]propyl]-4-hydroxy-α-[(1-oxo-2-cyclohexylethyl)amino]benzenepropanamide tris(trifluoroacetate)

Yield: 57%. $^1$H NMR: δ 4.41 (t, $^3J$ = 7.8, α-CH), 6.71 (m, 2 H) and 7.06 (m, 2 H) (aromatic H), 0.80-0.92 (m, 2 H), 1.12-1.23 (m, 3 H), 1.48 (m, 1 H) and 1.57-1.68 (m, 5 H) (CH and $CH_2$ of the diamine and the cyclohexylacetyl moiety), 1.80 (m, 2-, 6- and 8-$CH_2$), 2.08 (m, 11-$CH_2$ and 2-$CH_2$ of the cyclohexylacetyl moiety), 2.79-3.28 (m, 14H, β-$CH_2$ and the remaining $CH_2$ of the polyamine moiety). $^{13}$C NMR: δ 24.3, 24.4, 25.4, 27.2, 27.3, 27.3, 27.4, 34.0, 34.2, 36.8, 37.8, 37.9, 44.9, 45.9, 46.3, 48.2, 48.3, 57.0, 116.3 (2 C), 129.0, 131.3 (2 C), 157.5, 175.2, 175.7. HPLC-ELS: 99.3%. MS (ES): 490.4 (M+1).

**Example 2.2**

General synthetic procedure

A resin bound diamine (1.0 mmol) was suspended in $CH_2Cl_2$ (25 mL). Diisopropylethylamine (DIEA) (6.0 mmol) and 2-nitrobenzenesulfonyl chloride (4.0 mmol) were added successively

and the reaction mixture was stirred under nitrogen at room temperature for 3 h. The resin was drained, washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL) and dried *in vacuo*.

The above resin (0.92 mmol) was suspended under nitrogen in dry THF/$CH_2Cl_2$ (1:1) (11.0 mL). A solution of a *N*-(Trimethylsilyl)ethoxycarbonyl amino alcohol (4.61 mmol) in dry THF/$CH_2Cl_2$ (1:1) (6.0 mL), tributylphosphine (4.61 mmol) and ADDP (4.61 mmol) in dry THF/$CH_2Cl_2$ (1:1) (6.0 mL) were added successively. The mixture was stirred at room temperature under nitrogen for 3 h. The resin was drained and washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL) and dried *in vacuo*. The procedure was repeated twice, and the resulting resin was dried *in vacuo*.

The above resin (0.74 mmol) was suspended in dry THF (30 mL) under nitrogen in a flask equipped with a thermometer. A solution of TBAF (1M in THF, 3.69 mmol) was added slowly, and the mixture stirred at 50°C for 30 min. The reaction mixture was cooled to room temperature, the resin filtered off and washed with with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL) and dried *in vacuo*.

A solution of (*S*)-*N*-Fmoc-*O*-(*tert*-butyl)tyrosine (1.08 mmol) and HATU (1.08 mmol) in DMF (2 mL), followed by a solution of collidine (1.62 mmol) in DMF (1 mL), was added to the resin (0.27 mmol) placed in a syringe. The mixture was agitated for 2 h at room temperature, and the resin was subsequently washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL). The product was treated with 20% piperidine in DMF (v/v, 5.0 mL) and the mixture agitated for 3 min at room temperature. The resulting resin was washed with DMF (3 x 5 mL), treated again with 20% piperidine in DMF (5.0 mL) for 20 min and then washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL). The resulting resin was treated with a solution of butyric acid (1.08 mmol) and HATU (1.08 mmol) in DMF (2 mL), followed by a solution of collidine (1.62 mmol) in DMF (1 mL). The mixture was agitated for 2 h at room temperature and the resulting resin washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL).

The resin (0.27 mmol) was treated with DBU (1.35 mmol) in DMF (2 mL) and mercaptoethanol (1.35 mmol) in DMF (2 mL) for 30 min. The resin was drained, washed with DMF (5 x 5 mL) and the procedure was repeated agitating for 5 min. The resin was washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL) and then treated with a solution of $CH_2Cl_2$/TFA/triisopropylsilane/$H_2O$ (47.5:47.5:2.5:2.5 v/v, 5 mL) for 2 h. The resin was drained and washed with MeOH (2 x 5 mL) and $CH_2Cl_2$ (2 x 5 mL). The solution of the cleaved product and the washings were combined and evaporated *in vacuo* to a sticky solid which was triturated with diethyl ether and purified by preparative HPLC to give the final product as a clear gum.

**The following compounds were prepared according to the general procedure**

**2g**, (*S*)-*N*-[5-[6-Aminohexyl)amino]pentyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 0.85 (t, $J$ = 7.4 Hz, 3H), 1.22–1.69 (m, 16H), 2.16 (t, $J$ = 7.3 Hz, 2H), 2.80 (dd, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 8.0 Hz, 1H), 2.84–3.23 (m, 9H), 4.45 (t, $J$ = 7.6 Hz, 1H), 6.70 and 7.05 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 16.0, 22.3, 26.7, 28.8, 29.0, 29.1, 30.4, 31.7, 40.4, 40.8, 41.9, 42.6, 58.8, 118.3, 131.2, 133.4, 159.3, 175.9, 178.0. HPLC-ELS: 99.9%. HRMS (MALDI): $C_{24}H_{42}N_4O_3$ requires M + 1 at *m/z* 434.3257; found 434.3261.

**2h**, (*S*)-*N*-[9-[2-Aminoethyl)amino]nonyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 0.84 (t, $J$ = 7.5 Hz, 3H), 1.15–1.78 (m, 16H), 2.15 (t, $J$ = 7.6 Hz, 2H), 2.77 (dd, $J_{AX}$ = 8.4 Hz, $J_{AB}$ = 13.0 Hz, 1H), 2.98 (dd, $J_{BX}$ = 6.9 Hz, $J_{AB}$ = 13.0 Hz, 1H), 3.03–3.13 (m, 8H), 4.66 (t, $J$ = 7.3 Hz, 1H), 6.68 and 7.03 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 12.3, 18.7, 25.7, 25.8, 26.2, 28.5, 28.6, 28.7, 28.7, 35.3, 36.9, 37.2, 38.8, 44.1, 55.0, 114.7, 127.7, 129.9, 155.0, 172.4, 174.6. HPLC-ELS: 99.3%. HRMS (MALDI): $C_{24}H_{42}N_4O_3$ requires M + 1 at *m/z* 434.3257; found 434.3260.

**2i**, (*S*)-*N*-[7-[4-Aminobutyl)amino]heptyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 0.85 (t, $J$ = 7.5 Hz, 3H), 1.21–1.76 (m, 16H), 2.15 (t, $J$ = 7.8 Hz, 2H), 2.74–3.24 (m, 10H), 4.45 (t, $J$ = 6.9 Hz, 1H), 6.69 and 7.04 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 12.3, 18.7, 22.7, 24.1, 25.6, 25.8, 25.9, 28.2, 29.5, 36.8, 37.2, 38.5, 38.6, 55.1, 114.8, 127.7, 129.9, 156.0, 172.4, 174.6. HPLC-ELS: 100.0%. $C_{24}H_{42}N_4O_3$ requires M + 1 at *m/z* 434.3257; found 434.3265.

**2j**, (*S*)-*N*-[6-[5-Aminopentyl)amino]hexyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 0.85 (t, $J$ = 7.5 Hz, 3H), 1.22–1.76 (m, 16H), 2.15 (t, $J$ = 7.6 Hz, 2H), 2.72–3.20 (m, 10H), 4.45 (t, $J$ = 7.7 Hz, 1H), 6.69 and 7.04 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 12.3, 18.7, 22.9, 25.2, 25.5, 25.6, 25.6, 26.5, 28.4, 36.8, 37.2, 38.5, 38.8, 55.1, 114.8, 127.7, 129.9, 156.0, 172.4, 174.6. HPLC-ELS: 98.9%. HRMS (MALDI): $C_{24}H_{42}N_4O_3$ requires M + 1 at *m/z* 434.3257; found 434.3272.

**2k**, (*S*)-*N*-[4-[7-Aminoheptyl)amino]butyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 0.84 (t, $J$ = 7.3 Hz, 3H), 1.41–1.69 (m, 16H), 2.16 (t, $J$ = 7.3 Hz, 2H), 2.80 (dd, $J_{AB}$ = 13.8 Hz, $J_{AX}$ = 8.5 Hz, 1H), 2.89–3.19 (m, 9H), 4.43 (t, $J$ = 8.5 Hz, 1H), 6.71 and 7.05 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 14.3, 20.6, 24.8, 27.6, 27.7, 28.8, 30.0, 38.7, 39.1, 39.7, 41.1, 57.3, 116.7, 129.5, 131.7, 157.7, 174.5, 176.5. HPLC-ELS: 99.7%. HRMS (MALDI): $C_{24}H_{42}N_4O_3$ requires M + 1 at *m/z* 434.3257; found 434.3263.

**Example 2.3**

General synthetic procedure

A solution of (*S*)-*N*-Fmoc-*O*-(*tert*-butyl)tyrosine (1.08 mmol) and HATU (1.08 mmol) in DMF (2 mL), followed by a solution of collidine (1.62 mmol) in DMF (1 mL), was added to resin bound 8-[(2-nitrophenyl)sulfonyl]-3-[aminopropyl]amino]octylamine (0.27 mmol)

placed in a syringe. The mixture was agitated for 2 h at room temperature, and the resin was subsequently washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL). The product was treated with 20% piperidine in DMF (v/v, 5.0 mL) and the mixture agitated for 3 min at room temperature. The resulting resin was washed with DMF (3 x 5 mL), treated again with 20% piperidine in DMF (5.0 mL) for 20 min and then washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL). The resulting resin was treated with a solution of an acid (1.08 mmol) and HATU (1.08 mmol) in DMF (2 mL), followed by a solution of collidine (1.62 mmol) in DMF (1 mL). The mixture was agitated for 2 h at room temperature and the resulting resin washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL).

The resin (0.27 mmol) was treated with DBU (1.35 mmol) in DMF (2 mL) and mercaptoethanol (1.35 mmol) in DMF (2 mL) for 30 min. The resin was drained, washed with DMF (5 x 5 mL), and the procedure was repeated agitating for 5 min. The resin was washed with DMF (3 x 5 mL), $CH_2Cl_2$ (3 x 5 mL), MeOH (3 x 5 mL) and $CH_2Cl_2$ (3 x 5 mL) and then treated with a solution of $CH_2Cl_2$/TFA/triisopropylsilane/$H_2O$ (47.5:47.5:2.5:2.5 v/v, 5 mL) for 2 h. The resin was drained and washed with MeOH (2 x 5 mL) and $CH_2Cl_2$ (2 x 5 mL). The solution of the cleaved product and the washings were combined and evaporated *in vacuo* to a sticky solid which was triturated with diethyl ether and purified by preparative HPLC to give the final product as a clear gum.

**21**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenylmethyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 1.18–1.44 (m, 10H), 1.68 (t, $J$ = 7.8 Hz, 2H), 2.07 (t, $J$ = 7.9 Hz, 2H), 2.96–3.12 (m, 10H), 4.69 (t, $J$ = 7.0 Hz, 1H), 6.71 and 7.09 (AA'BB' system, aromatic H), 7.44 (dd, $J$ = 7.44 Hz, $J$ = 7.2 Hz, 2H), 7.52 (dd, $J$ = 7.6 Hz, $J$ = 7.6 Hz, 1H), 7.76 (d, $J$ = 7.9 Hz, 2H). $^{13}$C NMR ($CD_3OD$): $\delta$ 28.3, 30.0, 30.3, 30.6, 32.9, 33.1, 40.8, 41.3, 43.3, 43.4, 48.7, 60.2, 119.2, 131.4, 132.1, 132.5, 134.3, 135.8, 138.3, 160.3, 172.9, 176.7. HPLC-ELS: 98.1%. $C_{27}H_{40}N_4O_3$ requires M + 1 at *m/z* 468.3100; found 468.3100.

**2m**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-2-ethyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$1.30–1.41 (m, 10H), 1.67 (m, 2H), 2.06–2.10 (m, 2H), 2.80 (dd, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 7.8 Hz, 1H), 2.96–3.13 (m, 10H), 3.48 (d, $J$ = 13.5 Hz, 1H), 3.52 (d, $J$ = 13.5 Hz, 1H), 4.49 (t, $J$ = 7.0 Hz, 1H), 6.67 (d, $J$ = 6.5 Hz, 2H), 6.98 (d, $J$ = 6.5 Hz, 2H), 7.13 (d, $J$ = 6.9 Hz, 2H), 7.21–7.27 (m, 4H). $^{13}$C NMR ($CD_3OD$): $\delta$25.7, 27.5, 27.8, 28.0, 30.3, 30.5, 38.3, 38.8, 40.7, 44.0, 46.2, 57.0 116.7, 128.3, 129.3, 130.0, 130.5, 131.7, 137.0, 157.7, 173.9, 174.2. HPLC-ELS: 99.7%. HRMS (MALDI): $C_{28}H_{342}N_4O_3$ requires M + 1 at *m/z* 482.3257; found, 482.3251.

**2n**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-3-propyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$1.18–1.40 (m, 10H), 1.66–1.71 (m, 2H), 2.06 (m, 2H), 2.47 (t, $J$ = 7.2 Hz, 2H), 2.73 (dd, $J_{AX}$ = 7.8 Hz, $J_{AB}$ = 14.0 Hz, 1H), 2.82 (t, $J$ = 8.1 Hz, 2H), 2.90 (dd, $J_{AX}$ = 7.2 Hz, $J_{AB}$ = 14.0 Hz, 1H), 3.00–3.13 (m, 7H), 4.41 (t, $J$ = 7.2 Hz,1H), 6.68 and 7.00 (AA'BB' system, aromatic H), 7.14, (d, $J$ = 8.1 Hz, 2H), 7.16 (dd, $J$ = 7.1 Hz, $J$ = 1.2 Hz, 1H), 7.24 (ddd, $J$ = 7.5 Hz, $J$ = 7.5 Hz, $J$ = 1.8 Hz, 2H). $^{13}$C NMR ($CD_3OD$): $\delta$25.6, 25.9, 26.1, 28.5, 28.5, 28. 6, 31.2, 36.3, 36.9, 37.1, 38.7, 44.2, 55.1, 64.8, 114.8, 125.8, 127.6, 128.0, 128.1, 129.9, 140.8, 155.8, 156.0, 172.2, 173.7. HPLC-ELS: 100.0%. $C_{29}H_{44}N_4O_3$ requires M + 1 at *m/z* 496.3413; found 496.3405.

**2o**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-3-prop-2-enyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$1.18 (t, $J$ = 7.1 Hz, 2H), 1.22–1.40 (m, 8H), 1.68 (t, $J$ = 7.5 Hz, 2H), 2.07 (t, $J$ = 7.8 Hz, 2H), 2.84–3.17 (m, 10H), 3.61 (q, $J$ = 7.1 Hz, 1H), 4.60 (t, $J$ = 7.5 Hz, 1H), 6.67 (d, $J$ = 15.7 Hz, 1H), 6.71 and 7.07 (AA'BB' system, aromatic H), 7.39 (d, $J$ = 7.0 Hz, 2H), 7.50 (d, $J$ = 15.8 Hz, 1H), 7.55 (d, $J$ = 7.8 Hz, 1H). $^{13}$C NMR ($CD_3OD$): $\delta$28.3, 30.1, 30.3, 30.6, 32.9, 33.1, 40.8, 41.5, 43.3, 48.7, 59.8, 61.3, 119.2, 124.4, 131.8, 131.9, 133.8, 134.2, 139.2, 160.3, 171.2, 176.4. HPLC-ELS: 99.8%. $C_{29}H_{44}N_4O_3$ requires M + 1 at *m/z* 494.3257; found 494.3279.

**2p**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-2-yl-1-oxometyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$1.17–1.46 (m, 10H), 1.69 (m, 2H), 2.04–2.10 (m, 2H), 2.99–3-22 (m, 10H), 4.69 (t, $J$ = 7.0 Hz, 1H), 6.69 and 7.06 (AA'BB' system, aromatic H), 7.55 (m, 1H), 7.95 (m, 1H), 8.05 (d, $J$ = 7.5 Hz, 1H), 8.62 (d, $J$ = 4.5 Hz, 1H). $^{13}$C NMR ($CD_3OD$): $\delta$26.3, 28.0, 28.3, 28.6, 30.9, 31.0, 38.8, 39.9, 41.3, 46.7, 57.4, 117.2, 119.7, 128.9, 129.5, 132.4, 130.4, 146.5, 151.4, 158.4, 166.9, 174.1. HPLC-ELS: 99.8%. HRMS (MALDI): $C_{26}H_{39}N_5O_3$ requires M + 1 at *m/z* 469.3053; found, 469.3050.

**2q**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-3-yl-1-oxomethyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$1.18–1.45 (m, 10H), 1.68 (m, 2H), 2.04–2.10 (m, 2H), 2.96–3-15 (m, 10H), 4.69 (t, $J$ = 7.0 Hz, 1H), 6.70 and 7.10 (AA'BB' system, aromatic H), 7.74 (dd, $J$ = 8.0 Hz, $J$ = 5.5 Hz, 1H), 8.45 (d, $J$ = 8.5 Hz, 1H), 8.78 (d, $J$ = 5.0 Hz, 1H), 9.01 (s, 1H). $^{13}$C NMR ($CD_3OD$): $\delta$24.4, 25.7, 26.2, 26.5, 26.8, 29.1, 29.2, 36.9, 37.4, 39.6, 47.6, 56.5, 115.4, 115.8, 118.1, 125.1, 128.1, 130.4, 131.9, 138.8, 146.5, 149.5, 156.5, 165.6, 172.4. HPLC-ELS: 99.5%. HRMS (MALDI): $C_{26}H_{39}N_5O_3$ requires M + 1 at *m/z* 469.3053; found, 469.3056.

**2r**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-4-yl-1-oxomethyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$1.24–1.43 (m, 10H), 1.65–1.74 (m, 2H), 2.04–2.12 (m, 2H), 2.98–3.19 (m, 10H), 4.74 (t, $J$ = 8.0 Hz, 1H), 6.72 and 7.10 (AA'BB' system, aromatic H), 8.16 (d, $J$ = 6.5 Hz, 2H), 8.91 (d, $J$ = 6.5 Hz, 2H). $^{13}$C NMR ($CD_3OD$): $\delta$25.7, 27.5, 27.8, 28.1, 30.4, 30.4, 38.3, 38.7, 40.9, 41.0, 46.2, 57.9, 114.8, 116.7, 125.3, 129.3, 131.8, 147.6, 157.8, 166.5, 173.7. HPLC-ELS: 99.8%. HRMS (MALDI): $C_{26}H_{39}N_5O_3$ requires M + 1 at *m/z* 469.3053; found, 469.3066.

**2s**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxo-cyclohexylmethyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 1.22–1.42 (m, 16H), 1.40–1.71 (m, 7H), 2.07 (t, $J$ = 7.6 Hz, 2H), 2.19 (t, J = 7.5 Hz, 1H), 2.75 (dd, $J_{AB}$ = 8.3 Hz, $J_{AX}$ = 14.0 Hz, 1H), 2.92 (dd, $J_{AB}$ = 6.9 Hz, $J_{AX}$ = 14.0 Hz, 1H), 2.99–3.14 (m, 8H), 4.46 (t, $J$ = 7.8 Hz, 1H), 6.69 and 7.03 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 26.7, 27.9, 28.1, 28.2, 28.4, 28.7, 29.0, 31.3, 31.5, 31.6, 32.1, 39.1, 39.8, 41.6, 47.1, 47.4, 57.6, 117.5, 130.4, 132.6, 158.6, 175.0, 180.1. HPLC-ELS: 96.1%. HRMS (MALDI): $C_{27}H_{46}N_4O_3$ requires M + 1 at *m/z* 474.3570; found, 474.3573.

**2t**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxoethyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 1.32–1.69 (m, 16H), 1.92 (s, 3H), 2.03–2.08 (m, 6H), 2.80 (dd, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 8.0 Hz, 1H), 2.98–3.13 (m 9H), 4.45 (t, $J$ = 8.0 Hz, 1H), 6.70 and 7.04 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 22.9, 25.7, 27.0, 27.5, 27.8, 28.0, 30.5, 30.5, 38.2, 38.8, 40.7, 40.9, 46.2, 57.2, 116.6, 129.5, 131.7, 157.7, 173.4, 174.0. HPLC-ELS: 99.7%. HRMS (MALDI): $C_{22}H_{38}N_4O_3$ requires M + 1 at *m/z* 406.2944; found, 406.2947.

**2u**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxopropyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 1.04 (t, $J$ = 7.7 Hz, 3H), 1.20–1.47 (m, 10H), 1.69 (m, 2H), 2.07 (m, 2H), 2.19 (q, $J$ = 7.7 Hz, 2H), 2.80 (dd, $J_{AB}$ = 13.8 Hz, $J_{AX}$ = 8.0 Hz, 1H), 2.94–3.18 (m, 10H), 4.46 (t, $J$ = 7.3 Hz, 1H), 6.70 and 7.04 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 10.7, 25.8, 27.5, 27.8, 28.1, 30.4, 30.5, 38.3, 38.9, 40.7, 46.2, 57.0, 117.0, 129.5, 131.7, 157.7, 174.1, 177.1. HPLC-ELS: 98.5%. HRMS (MALDI): $C_{23}H_{40}N_4O_3$ requires M + 1 at *m/z* 420.3100; found, 420.3099.

**2v**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxohexyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.27–1.41 (m, 16H), 1.52 (m, 2H), 2.08 (m, 2H), 2.17 (t, $J$ = 7.0 Hz, 2H), 2.78 (dd, $J_{AB}$ = 13.6 Hz, $J_{AX}$ = 7.0 Hz, 1H), 2.99–3.31 (m, 8H), 4.48 (t, $J$ = 7.0 Hz, 1H), 6.70 and 7.04 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$ 14.6, 23.8, 25.8, 27.0, 27.5, 27.8, 28.1, 30.4, 30.4, 30.6, 32.8, 37.3, 38.3, 38.8, 40.7, 46.2, 48.9,

56.9, 116.6, 129.5, 131.7, 157.7, 174.1, 176.5. HPLC-ELS: 99.2%. HRMS (MALDI): $C_{26}H_{46}N_4O_3$ requires M + 1 at *m/z* 462.3570; found, 462.357.

**2x**, (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxo-3-dimethylbutyl)amino]benzenepropaneamide bis(trifluoroacetate)

$^1$H NMR ($CD_3OD$): $\delta$ 1.11 (s, 9H), 1.23–1.44 (m, 10H), 1.69 (m, 2H), 2.08 (m, 2H), 2.84 (dd, JAB = 13.6 Hz, JAX = 7.0 Hz, 1H), 2.96–3.17 (m, 9H), 4.50 (t, J = 7.0 Hz, 1H), 6.70 and 7.05 (AA'BB' system, aromatic H). $^{13}$C NMR ($CD_3OD$): $\delta$24.7, 26.5, 26.8, 27.0, 29.4, 29.6, 37.2, 37.8, 39.1, 39.7, 45.2, 55.7, 116.0, 128.3, 130.8, 156.8, 173.1, 180.2. HPLC-ELS: 99.8%. HRMS (MALDI): $C_{25}H_{44}N_4O_3$ requires M + 1 at *m/z* 448.3413; found, 448.3418.

**Pharmacological Testing**

The philanthotoxin analogues under study were tested at non-NMDA (AMPA and kainate) receptors. Responses of voltage-clamped ($V_H$ = - 80mV) *Xenopus* oocytes, injected with rat brain RNA, were compared in the absence and presence of the substituted polyamine derivatives. The agonist kainate was applied to the voltage-clamped oocytes for different periods of time, and the relationship between periods of application and potency of the philanthotoxin antagonists was determined.

**Non-NMDAR assay**

*Xenopus laevis* oocytes were injected with rat brain RNA and incubated at 18 °C for at least 3 days (Brackley et al. *J. Pharmacol. Exp. Ther.* **1993**, *266*, 1573-1580). Single oocytes were transferred to a perfusion bath and continuously perfused with saline containing 120 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 10 mM HEPES (pH adjusted to 7.5 with NaOH). The oocytes were voltage-clamped at –80 mV using an Axoclamp 2A (Axon Instruments) and current output was digitized with a Sony PCM and recorded to videotape with a Sony VCR. For the short application, responses of non-NMDAR were elicited by perfusion of 100 μM kainic acid for 120 s. PhTX-343 analogues were co-applied for 40 s during this kainic acid application. For the

longer application, kainic acid (100 μM) was applied for 40 s, during which time a stable current was achieved. PhTX analogues were then co-applied until another stable current was obtained, the application time (up to 120 s) depending on the antagonism onset rate of the analogue. Antagonism was measured by comparing the stable currents before and during PhTX application.

**GluR1 assay**

**Electrophysiology**

3-5 ovarian lobes were surgically removed from anesthetized *Xenopus laevis*. The removed ovaries were treaded with collagenase type A (1mg/mL, Boehringer) for 2-3 h at 20°C in buffer OR-2 (88 mM NaCl, 1.1 mM KCl, 2.4 mM $NaHCO_3$, 0.8 mM $MgCl_2$ and 15 mM HEPES-NaOH pH 7.6) and oocytes at stage V or VI were isolated. Oocytes were maintained in Barth's solution and injected the day after isolation with 5-30 ng cRNA and maintained in Barth's solution (Buffer OR-2 supplemented with 0.3 mM $Ca(NO_3)_2$, 0.3 mM $CaCl_2$, 100 μg/ml gentamycin, 100 IU/ml pencillin and 100 μg/mL streptomycin). Oocytes were recorded in Ringer solution (115 mM NaCl, 2.5 mM KCl, 1.8 mM $CaCl_2$, 0.1 mM $MgCl_2$ and 10 mM HEPES-NaOH pH 7.5) 3-14 days postinjection using a two electrode voltage clamp (Warner OC-725C). The pipettes had a resitance of 0.7-2 MΩ and were filled with 3 M KCl. Oocytes were clamped at -100 - -20 mV and for oocytes exhibiting high currents the recordings were performed in low $Ca^{2+}$ Ringer (115 mM NaCl, 2.5 mM, KCl, 0.1 mM $CaCl_2$, 1.8 mM $MgCl_2$ and 10 mM HEPES-NaOH pH 7.5) to avoid activation of the $Ca^{2+}$ activated Cl current.

**cRNA syntesis**

Fragments containing only the coding regions of the different glutamate receptors were generated by PCR and cloned into pGEMHE. The clones were verified by sequencing. *In vitro* cRNA transcripts were generated as runoff transcription on 20 μg/mL linerized plasmids by incubation in 40 mM Tris-HCl, pH 7.8, 8 mM $MgCl_2$, 2 mM spermidine, 50 mM NaCl, 3.5 mM DTT, 0.5 mM ATP, 0.5 mM UTP, 0.5 mM CTP, 0.1 mM GTP, 0.5 mM GpppG and 0.5 U/μL T7 polymerase for 90 min in the presence of trace amounts of [$^{32}$P]UTP for quantification of the cRNA.

**NMDAR assay**

*Xenopus laevis* oocytes were injected with rat brain RNA and incubated at 18 °C for at least 3 days (Brackley et al. *J. Pharmacol. Exp. Ther.* 1993, *266*, 1573-1580). Single oocytes were transferred to a perfusion bath and continuously perfused with saline containing 120 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 10 mM HEPES (pH adjusted to 7.5 with NaOH). The oocytes were voltage-clamped at –80 mV using an Axoclamp 2A (Axon Instruments) and current output was digitized with a Sony PCM and recorded to videotape with a Sony VCR. Responses of NMDAR were elicited by perfusion of 100 μM NMDA plus 10 μM Gly for 120 s. PhTX-343 analogues were co-applied from 40-80 s of this application.

**nAChR assay**

The nAChR assay was performed essentially as previously described (Strømgaard et al. *J. Med. Chem.* **1999**, *42*, 5224-5234; Shao et al. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 1269-1276). TE671 cells were grown in Petri dishes and transferred to a perfusion bath mounted on the stage of an inverted microscope. Patch pipettes filled with 140 mM CsCl, 1 mM $CaCl_2$, 11 mM EDTA, and 5mM HEPES (pH adjusted to 7.2 with 1 M CsOH) were used for whole-cell recording. Cells were constantly perfused at ca. 5 mL/min with saline containing 135 mM NaCl, 5.4 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 5 mM HEPES (pH adjusted to 7.4 with 3 M NaOH). Ligands (10 μM acetylcholine alone or 10 μM acetylcholine plus test compound) were applied as 1 s pulses at intervals of at least 30 s to allow the nAChR to recover from the desensitizing effect of agonist and the blocking effect of the antagonist. Whole-cell currents were monitored using an Axopatch 200 patch-clamp amplifier (Axon Instruments) and the output recorded on the hard disk of a PC using pClamp 5.7.2 software (Axon Instruments). Whole-cell recordings were performed at ambient laboratory temperature (17-23 °C).

## Pharmacological Results

| Analogue | $IC_{50}$ ± SE (μM) (number of oocytes/cells) | | | |
|---|---|---|---|---|
| | NMDAR* | non-NMDAR** | | nAChR*** |
| | | Short application | Long application | |
| **1** | 2.95 ± 0.18 (9) | - | 0.032 ± 0.003 (7) | 3.38 ± 0.22 (13) |
| **2e** | 0.13 ± 0.03 (2) | 0.015 ± 0.004 (10) | 0.012 ± 0.002 (5) | 22.3 ± 1.4 (10) |
| **2f** | 0.42 ± 0.007 (10) | 0.18 ± 0.12 (4) | 0.0039 ± 0.0007 (7) | 13.2 ± 2.0 (11) |
| PhTX-343 | 2.03 ± 0.31 (6) | 0.75 ± 0.08 (5) | 0.55 ± 0.12 (9) | 13.8 ± 2.3 (22) |

* Inhibition of responses of rat brain RNA injected oocytes to 100 μM NMDA plus 10 μM Gly at $V_H$ = -80 mV.

** Inhibition of responses of rat brain RNA injected oocytes to 100 μM KA at $V_H$ = -80 mV.

*** Inhibition of responses of TE671 cells (end data) to 10 μM ACh at $V_H$ = -100 mV.

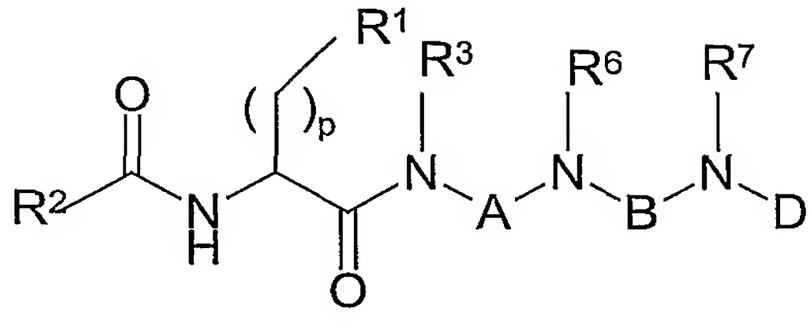
| Analogue | $IC_{50}$ (μM) | |
|---|---|---|
| | AMPA (GluR1)* | |
| | -40 mV | -80 mV |
| **2g** | 0.287 | 0.0058 |
| **2i** | 3 | 0.168 |
| **2j** | 14 | 0.468 |
| **2k** | 0.135 | 0.026 |
| **2l** | 0.258 | 0.121 |
| **2m** | 0.255 | 0.102 |
| **2n** | 0.255 | 0.261 |
| **2o** | 0.258 | 0.106 |
| **2p** | 0.176 | 0.130 |
| **2q** | 0.212 | 0.087 |
| **2r** | 0.272 | 0.065 |
| **2s** | 0.245 | 0.080 |
| **2t** | 0.300 | 0.237 |
| **2u** | 0.300 | 0.106 |
| **2v** | 0.666 | 0.068 |
| **2x** | 0.148 | 0.090 |

* Inhibition of responses of oocytes injected with GluR1 flop RNA to 100 μM Glu at $V_H$ = -40 mV and –80mV, respectively.

The results indicate the potency of the compounds towards the AMPA receptor. The compounds of the present invention are potent in the nano- to micromolar range. As the results also indicate, the compounds of the present invention are use-dependent inhibitors of the AMPA receptor.

**Claims:**

1. A compound represented by the general formula I



I

wherein

$R^1$ represents a partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms, an aryl or a heteroaryl, all of which may be substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkylthio, $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl, aryl, heteroaryl, wherein aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; $NR^8R^9$, wherein $R^8$ and $R^9$ independently represent hydrogen, $C_{1-6}$-alkyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, or $R^8$ and $R^9$ together form a ring which may optionally contain further nitrogen, oxygen or sulfur atoms, and which may be partly saturated;

p is 0, 1, 2 , 3 or 4;

$R^2$ represents hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$-alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

$R^3$, $R^6$ and $R^7$ independently represent hydrogen or $C_{1-6}$-alkyl;

**A** and **B** independently represent $-(CH_2)_nX(CH_2)_m-$, wherein X represents $-CR^4R^5$, O or S, wherein $R^4$ and $R^5$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; n is 0-12 and m is 0-12 with the proviso that $1 \leq n+m \leq 12$ and when X represents O or S then $n \geq 2$ and $m \geq 2$;

**D** represents hydrogen, $C_{1-6}$-alkyl or $-(CH_2)_oY(CH_2)_qNR^{10}R^{11}$, wherein Y represents $-CR^{12}R^{13}$, O or S, wherein $R^{12}$ and $R^{13}$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; o is 1-12 and q is 1-12 with the proviso that $1 \leq o+q \leq 12$, and when Y represents O or S then $o \geq 2$ and $q \geq 2$; $R^{10}$ and $R^{11}$ independently represent hydrogen or $C_{1-6}$-alkyl;

or a pharmaceutically acceptable addition salt thereof;

2. The compound according to formula I in claim 1, wherein $R^1$ represents a partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms, an aryl or a heteroaryl, all of which may be substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkylthio, $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl, aryl, heteroaryl, wherein aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; $NR^8R^9$, wherein $R^8$ and $R^9$ independently represent hydrogen, $C_{1-6}$-alkyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, or $R^8$ and $R^9$ together form a ring which may optionally contain further nitrogen, oxygen or sulfur atoms and which may be partly saturated;

p is 0, 1, 2 , 3 or 4;

$R^2$ represents $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$-alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

$R^3$, $R^6$ and $R^7$ independently represent hydrogen or $C_{1-6}$-alkyl;

**A** and **B** independently represent $-(CH_2)_nX(CH_2)_m-$, wherein X represents $-CR^4R^5$, O or S, wherein $R^4$ and $R^5$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein

aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; n is 0-12 and m is 0-12 with the proviso that $1 \leq n+m \leq 12$ and when X represents O or S then $n \geq 2$ and $m \geq 2$;

**D** represents hydrogen, $C_{1-6}$-alkyl, or $-(CH_2)_oY(CH_2)_qNR^{10}R^{11}$, wherein Y represents $-CR^{12}R^{13}$, O or S, wherein $R^{12}$ and $R^{13}$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; o is 1-12 and q is 1-12 with the proviso that $1 \leq o+q \leq 12$, and when Y represents O or S then $o \geq 2$ and $q \geq 2$; $R^{10}$ and $R^{11}$ independently represent hydrogen or $C_{1-6}$-alkyl;

with the proviso that when $R^2$ is a 2-phenylethylene, benzyl, cyclohexyl or phenyl and p is 1, and D is $-(CH_2)_oY(CH_2)_qNR^{10}R^{11}$, wherein Y is $-CR^{12}R^{13}$ and $R^{10}$, $R^{11}$, $R^{12}$ and $R^{13}$ are all hydrogen, then $R^1$ is not phenyl substituted with OH in the 4-position;

3. The compound according to claim 1, wherein $R^1$ represents a partly or completely saturated 4-8-membered ring system which optionally contains from 2-4 heteroatoms, an aryl or a heteroaryl, all of which may be substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkylthio, $C_{1-6}$-alkylthio-$C_{1-6}$-alkyl, aryl, heteroaryl, wherein aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; $NR^8R^9$, wherein $R^8$ and $R^9$ independently represent hydrogen, $C_{1-6}$-alkyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, or $R^8$ and $R^9$ together form a ring which may optionally contain further nitrogen, oxygen or sulfur atoms and which may by partly saturated;

p is 0, 1, 2 , 3 or 4;

$R^2$ represents hydrogen, $C_{1-6}$-alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$-alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy;

$R^3$, $R^6$ and $R^7$ independently represent hydrogen or $C_{1-6}$-alkyl;

**A** and **B** independently represent $-(CH_2)_nX(CH_2)_m-$, wherein X represents $-CR^4R^5$, O or S, wherein $R^4$ and $R^5$ independently represent hydrogen, $C_{1-6}$-alkyl, aryl or benzyl, wherein aryl and benzyl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH or $C_{1-6}$-alkoxy; n is 0-12 and m is 0-12 with the proviso that $1 \leq n+m \leq 12$ and when X represents O or S then $n \geq 2$ and $m \geq 2$;

**D** represents hydrogen or $C_{1-6}$-alkyl, or a pharmaceutically acceptable addition salt thereof;

with the proviso, that the compound is not N-[8-[(3-aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide, N-[3-[(8-aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide, or N-[4-[(3-aminopropyl)amino]butyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropanamide;

4. The compound according to claim 1 wherein $R^2$ represents $C_{3-8}$-cycloalkyl, $C_{3-8}$-cycloalkyl-$C_{1-6}$-alkyl, aryl, heteroaryl, aryl-$C_{1-6}$-alkyl, heteroaryl-$C_{1-6}$-alkyl, aryl-$C_{2-6}$ alkenyl, heteroaryl-$C_{2-6}$ alkenyl, wherein the aryl and heteroaryl may be further substituted one or more times with halogen, $C_{1-6}$-alkyl, $C_{1-6}$-hydroxyalkyl, $CF_3$, CN, OH, SH, or $C_{1-6}$-alkoxy;

5. The compound according to any of the preceding claims, wherein $R^1$ represents an optionally substituted aryl or heteroaryl;

6. The compound according to any of the preceding claims, wherein D represents hydrogen or $C_{1-6}$-alkyl;

7. The compound according to any of the preceding claims, wherein A represents $-(CH_2)_nCH_2(CH_2)_m-$ and $3 \leq n + m \leq 8$;

8. The compound according to claim 7, wherein n + m is 7;

9. The compound according to any of the preceding claims, wherein p is 1;

10. The compound according to any of the preceding claims, wherein B represents $-(CH_2)_nCH_2(CH_2)_m-$ and $1 \leq n + m \leq 6$;

11. The compound according to claim 10 wherein $n + m$ is 2;

12. The compound according to any of the preceding claims, wherein A and B together represent carbon chains consisting of at least 8 carbon atoms.

13. The compound according to claim 12, wherein A and B together represent carbon chains consisting of at least 10 carbon atoms.

14. The compound according to claim 13, wherein A and B together represent carbon chains consisting of 11 carbon atoms.

15. The compound according to any of the above claims, said compound being
(*S*)-*N*-[7-[4-Aminobutyl)amino]heptyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate),
(*S*)-*N*-[6-[5-Aminopentyl)amino]hexyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate),
(*S*)-*N*-[4-[7-Aminoheptyl)amino]butyl]-4-hydroxy-α-[(1-oxobutyl)amino]benzenepropaneamide bis(trifluoroacetate),
(*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenylmethyl)amino]benzenepropaneamide bis(trifluoroacetate),
(*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-2-ethyl)amino]benzenepropaneamide bis(trifluoroacetate),
(*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-3-propyl)amino]benzenepropaneamide bis(trifluoroacetate),
(*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxophenyl-3-prop-2-enyl)amino]benzenepropaneamide bis(trifluoroacetate),

(*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-2-yl-1-oxometyl)amino]benzenepropaneamide bis(trifluoroacetate), (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-3-yl-1-oxomethyl)amino]benzenepropaneamide bis(trifluoroacetate), (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(pyridin-4-yl-1-oxomethyl)amino]benzenepropaneamide bis(trifluoroacetate),(*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxo-cyclohexylmethyl)amino]benzenepropaneamide bis(trifluoroacetate), (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxoethyl)amino]benzenepropaneamide bis(trifluoroacetate), (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxopropyl)amino]benzenepropaneamide bis(trifluoroacetate), (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxohextyl)amino]benzenepropaneamide bis(trifluoroacetate) or (*S*)-*N*-[8-[3-Aminopropyl)amino]octyl]-4-hydroxy-α-[(1-oxo-3-dimethylbutyl)amino]benzenepropaneamide bis(trifluoroacetate) or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising at least one compound according to any of the preceding claims, or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents;

17. The use of a compound according to any of the claims 1-15, for the manufacture of medicaments for treatment of diseases responsive to antagonists of the AMPA receptor;

18. The use according to claim 17, wherein the disease is selected from the group consisting of stroke, cerebral ischemia, spinal cord trauma, head trauma, Parkinson's disease, tardive dyskinesia, Alzheimer's Disease, Huntington's chorea, AIDS encephalopathy, amyotrophic lateral sclerosis, epilepsy, convulsion, spasms, hypoxia, hypoglycemic

neuronal damage, ocular damage, migraine headache, psychosis, pain, anxiety, emesis, retinal neuropathy and tinnitus;

19. A method for the treatment of diseases responsive to antagonists of the AMPA receptor comprising administering to a patient in need thereof an effective amount of a compound according to any of the claims 1-15;

20. The method according to claim 19, wherein the disease to be treated is selected from the group consisting of stroke, cerebral ischemia, spinal cord trauma, head trauma, Parkinson's disease, tardive dyskinesia, Alzheimer's disease, Huntington's chorea, AIDS encephalopathy, amyotrophic lateral sclerosis, epilepsy, convulsion, spasms, hypoxia, hypoglycemic neuronal damage, ocular damage, migraine headache, psychosis, pain, anxiety, emesis, retinal neuropathy, and tinnitus.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00548

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 237/22, A61K 31/16, A61P 25/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 9622962 A1 (THE TRUSTEES OF COLOMBIA UNIVERSITY IN THE CITY OF NEW YORK), 1 August 1996 (01.08.96) -- | 1-20 |
| X | American Chemical Society, Washington, DC, ACS Symposium Series 658, Paul A. Hedin et al: "Phytochemicals for Pest Control", Developed from a symposium sponsered by the ACS Division of Agrochemicals at the 1995 International Chemical Congress of Pacific Basin Societies", pages 340-353 -- | 1-20 |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 January 2001 | 30 -01- 2002 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Viveca Norén/BS<br>Telephone No. +46 8 782 25 00 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00548

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | The Journal of Pharmacology and Experimental Therapeutics, Volume 278, No. 2, 1996, Mark S. Washburn et al: Block of alpha-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptors by Polyamines and Polyamine Toxins", page 669-678 | 1-20 |
| | -- | |
| X | Chirality, Volume 12, 2000, Kristina Strømgaard et al: "Solid Phase Synthesis and Biological Evaluation of Enantiomerically Pure Wasp Toxin Analogues PhTX-343 and PhTX-12, page 93-102 | 1-20 |
| | -- | |
| X | WO 8907098 A1 (THE TRUSTEEES OF COLOMBIA UNIVERSITY IN THE CITY OF NEW YORK), 10 August 1989 (10.08.89) | 1-20 |
| | -- | |
| A | The Journal of Neuroscience, Volume 18, No. 20, 1998, Derek Bowie et al:"Activity-Dependent Modulation of Glutamate Receptors by Polyamines", pages 8175-8185 | 1-20 |
| | -- | |
| P,X | J. Med. Chem., Volume 43, 2000, Kristian Strømgaard et al: "Solid-Phase Synthesis and Biological Evaluation of a Combinatorial Library of Philanthotoxin Analogues", pages 4526-4533 | 1-20 |
| | -- | |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00548

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 1-14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

*ee next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*
Claims 19-20 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**
Present claims 1-14 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. Further did the initial phase of the search reveal a very large number of compounds relevant to the issue of novelty. It was therefore impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, documents disclosing only a limited number of the compounds which are relevant to the novelty of the present invention has been cited in this search report.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00548

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9622962 A1 | 01/08/96 | AU 5168496 A | 14/08/96 |
| | | US 6001824 A | 14/12/99 |
| WO 8907098 A1 | 10/08/89 | US 5770625 A | 23/06/98 |
| | | US 6001824 A | 14/12/99 |